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Intergenerational Transmission of Depression:
Clinical Observations and Molecular Mechanisms

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Abstract

Maternal mental illness can have a devastating effect during the perinatal period, and has a profound impact on the care that the baby receives and on the relationships that the baby forms. This review summarises clinical evidence showing the effects of perinatal depression on offspring physical and behavioural development, and on the transmission of psychopathology between generations. We then evaluate a number of factors which influence this relationship, such as genetic factors, the use of psychotropic medications during pregnancy, the timing within the perinatal period, the sex of the fetus, and exposure to maltreatment in childhood. Finally, we examine recent findings regarding the molecular mechanisms underpinning these clinical observations, and identify relevant epigenetic and biomarker changes in the glucocorticoid, oxytocin, estrogen and immune systems, as key biological mediators of these clinical findings. By understanding these molecular mechanisms in more detail, we will be able to improve outcomes for both mothers and their offspring for generations.

Introduction

The perinatal period represents a time in which substantial brain development of the offspring occurs: during pregnancy, where the fetal genetic makeup interacts with maternal biology, and postnatally, influenced by the primary caregiver for nourishment, security and emotional regulation^{1,2}. It is perhaps then no surprise that maternal mental disorders during this period, such as depression and postpartum psychosis, may have profound effects on the child's social, emotional, behavioural and cognitive development.

Maternal depression affects 10-15% of new mothers in both pregnancy and the postpartum period. It is associated with symptoms such as pervasive sadness, fatigue and rumination, which could impact mothers' ability to bond with the baby *in utero* or postnatally, which may lead to a lack of mothers' responsiveness to infant cues and to a disruption in the mother-child relationship.^{3,4} Postpartum psychosis is far less common than postpartum depression, occurring in 1-2 of 1000 childbearing women within the first 2-4 weeks after delivery⁵. It presents as early as 2-3 days after childbirth, with symptoms such as mood swings, confused thinking, grossly disorganised behaviour and paranoid, grandiose or bizarre delusions, and can severely impair the mother's ability to look after her child, often resulting in temporary separation.

There are consistent findings showing that the offspring of mothers suffering with perinatal mental health problems are more likely to have a psychopathology diagnosis in later life. This is likely to be influenced by the interplay of inherited genetic and epigenetic profiles, 'fetal programming', changes in neuroendocrine systems, and the experience of maternal care. This review starts by discussing clinical evidence of the effects of perinatal mental disorders on offspring outcomes, including the factors moderating this relationship, then explains some proposed biological mechanisms for this intergenerational transmission of psychopathology. Most of the evidence comes from studies on perinatal depression, although it is important to note that, in a majority of cases, perinatal depression is experienced together with clinically-significant anxiety³. It is therefore likely that the high arousal levels due to anxiety have a large contributory effect on parenting ability and perhaps on the biological mechanisms explained here, so this research has been included where appropriate. Much less research has been conducted on the consequences of postpartum psychosis on the offspring, and this evidence will be briefly considered in terms of the neuroendocrine and genetic alterations that accompany this disorder.

Clinical Evidence

Developmental Outcomes in Childhood

A mother's attachment to her baby can be strongly influenced by her experience of depressive symptoms, resulting in difficulty bonding and non-optimal maternal behaviours. In turn, a baby's early attachment relationship with the primary caregiver has a strong impact on its emotional regulation throughout development into adulthood⁶. Indeed, research suggests that offspring of depressed mothers typically show more behavioural difficulties⁷. The resulting attachment relationship can therefore be strained and affect multiple areas of the offspring's emotional, behavioural, cognitive and social development.

The main offspring abnormalities associated with perinatal psychopathology have been extensively reviewed before, for example recently by Stein and colleagues³. Hence, we concentrate here on reporting the most robust findings obtained in the largest available cohorts, which have usually investigated perinatal depression. These cohorts include: in the UK, the Avon Longitudinal Study of Parents and Children (ALSPAC)⁸⁻¹², a birth cohort study with 14,000 women recruited in pregnancy; in Canada, the National Longitudinal Survey of Children and Youth (NLSCY)^{13,14}, with over 35,000 children and their mothers, and the Quebec Longitudinal Study of Child Development (QLSCD)¹⁵, with over 2000 children; and, in the Netherlands, the Generation-R cohort¹⁶⁻¹⁸, with nearly 10,000 mothers recruited in Rotterdam, and the Tracking Adolescent's Individual Lives Survey (TRAILS)¹⁹ with a population of 2230.

The most robust findings from these large cohorts are summarised in Table 1: they demonstrate an overall increased risk of internalising and externalising difficulties, as well as of low IQ, in the children of mothers suffering from perinatal depression. Antenatal depression, but not postnatal, is also associated with increased risk of depression in the offspring that manifests in adolescence and young adulthood, as further discussed below. However, it must also be noted that many other studies, although often with smaller sample sizes, do not find any such significant associations^{20,21}, or even present contradictory findings²⁰. Some of these other studies, for example, have found that perinatal depression alone has no significant impact, but, when comorbid with perinatal anxiety, it impairs development of the offspring.

There are far fewer and smaller studies investigating the developmental impact on offspring of mothers experiencing psychotic symptoms. Interestingly, compared to women with depression, women with postpartum psychosis have no impairment in bonding, possibly because they do not share the same negative cognitions, and feelings of inadequacy and self-doubt, that influence the bonding experience of depressed mothers²². Still, mothers with psychosis appear similar to depressed mothers in interactive behaviour, with impaired responsiveness and less patience than mothers with no mental health problems, and one study found disturbances in both the bond to the infant and the interaction between mother and infant in this type of patient²³. Interestingly, when mothers have delusions that the baby might be in danger, they are more likely to show affectionate behaviour and normal competence and care for baby's basic needs; in contrast, when mothers have delusions that the baby is a devil or ill-fated, or is someone else's baby, they are more likely to have significant abusive incidents towards the baby²⁴. This points to an important role not just for the

diagnosis or the presence of symptoms, but also for the content of the symptoms that characterise the presentation.

[TABLE 1 AROUND HERE]

Psychopathology in Later Life

Research has recently focused on ‘intergenerational transmission’ of maternal psychopathology to offspring, resulting in psychopathology later in life. Various studies have found that maternal antenatal depression is linked with offspring depression in adolescence and young adulthood^{10,25}. The first study to describe this finding was the South London Child Development Study (SLCD), which includes 151 mother-child dyads and has found that adolescents exposed to antenatal depression have approximately 5-fold greater risk of depressive symptoms at age 16 than those not exposed²⁵. The subsequent, much larger ALSPAC cohort has reported the increased risk of adolescent offspring mental disorder at 2-fold, compared with controls²⁶, probably because it examines depressive symptoms in the community, as opposed to clinically-diagnosed depression in the SLCD study. A subsequent SLCD study paper has confirmed these findings when the offspring are young adults, at age 25²⁷. Antenatal depression also increases the risk of offspring being diagnosed with emotional disorders by age 16²⁸, and anxiety disorders by age 18²⁹. Finally, a recent study has shown that maternal mood symptoms during and after pregnancy are risk factors for the development of disruptive mood dysregulation disorder by 11 years³⁰.

These effects of antenatal depression are likely to be mediated, at least in part, by biological changes in the *in utero* environment, as we extensively discuss below. However, postnatal factors are also very important: one proposed mechanism for this ‘transmission’ of depression from parent to offspring is via impaired parenting³¹, as shown by behaviours such as parental withdrawal and parental intrusion³², which are more common in mothers suffering with mental health problems. In contrast, a good parental environment, showing low levels of maternal over-involvement and high maternal warmth, produces higher resilience in offspring³³.

Interestingly, children born before 32 weeks’ gestation are 3-fold more likely to have depressive disorder than those who grow to term³⁴, perhaps suggesting a further role for incomplete fetal development in the risk for psychopathology. As pre-term birth is associated with perinatal depression^{35,36}, this could be another mechanism by which depression is ‘transmitted’ from mother to offspring.

Potential Confounding Factors

Despite the evidence suggesting a link between perinatal depression and an increase in developmental impairment and psychopathology in offspring, this should not be interpreted as indicating a deterministic relationship, as there are several factors which may confound or moderate this association. These factors operate from pregnancy through to the early life of the offspring, with a broad range of consequences, from buffering against the negative impact of perinatal psychopathology, to exacerbating its effects. Some of the best-studied of these include the role of

genetics, maternal childhood maltreatment and use of antidepressants during pregnancy. These factors will be discussed below. Other less studied factors, including the role of the father, feeding habits and the timing of mental health problems, are reviewed in Stein's paper³.

Genetics

We cannot ignore the role of genetic inheritance in the intergenerational transmission of psychopathology, as a recent review on this topic clearly states³⁷. The genetic heritability of major depressive disorder is well-established, with particularly robust evidence coming from twin studies, reporting around 40% heritability in women and 30% in men³⁸. In addition to this, a major risk factor for adolescent psychopathology is family history, particularly parental depression³⁹. More recently, the genetic influences on postpartum depression have been established, with the most common genes relating to major depressive disorder, such as those involved in the metabolism of key neurotransmitters, also showing an association with postpartum depression⁴⁰ (some of the most robust findings are also discussed below, with reference to the relevant biological mechanisms). In addition, a genome-wide linkage study has identified the hemicentin 1 gene locus, to be associated with postpartum depressive symptoms⁴¹. Overall, one study recently reported that the heritability of perinatal depression as shown by a twin study design was 54%, whereas when using a sibling design, heritability was estimated at 44%. Interestingly, further analysis reported that 14% of the total variance in perinatal depression was unique for perinatal depression⁴².

It is likely that the genetic predispositions for major depressive disorder and perinatal depression overlap substantially, and thus it is difficult to disentangle this genetic inheritance effect from the impact of environmental factors, either because of transmission of heritable genetic variants, or because of the role of genetic variants as moderators of the effects of the prenatal environment, through gene x environment interactions.

In terms of transmission of heritable genetic risk from mothers to offspring, one approach that has attempted to disentangle this has been the use of a prenatal cross-fostering design including mothers either related or unrelated to their child as a result of *in vitro* fertilisation. In one such study, the reported association between prenatal stress and offspring outcomes show different genetic effects, i.e., prenatal maternal anxiety and depression predict offspring anxiety or antisocial behaviour in both related and unrelated mothers, while the link between prenatal stress and attention deficit hyperactivity disorder (ADHD) is explained solely by the genetic contribution⁴³.

A number of other study designs have confirmed that the intergenerational transmission of psychopathology is influenced, or moderated, by a genetic component. For example, the effects of low birth weight in increasing the risk of depression are stronger in children of depressed parents than in children with no such family history, indicating a genetic influence⁴⁴. Indeed, several genetic variants have been found to moderate the relationship between birth weight and children's social and emotional development, including classical 'psychiatric genes' such as the serotonin transporter⁴⁵ and the dopaminergic receptor D4⁴⁶. As depression in pregnancy is associated with low birth weight³⁵, it is likely that genetic variants also moderate the association between psychopathology in pregnancy and psychopathology in offspring. Indeed, recent reports found that a polygenic risk score for depression moderates the effects of antenatal depression on babies' brain

development in the first days of life⁴⁷, and a polygenic score based on genes coexpressed with the serotonin transporter predicts the effects of prenatal adversities on children's behavioural problems at 4-5 years⁴⁸. Interestingly, this latter polygenic score seems to identify children that are not only more susceptible to prenatal 'adverse' environment, but also more likely to benefit from a 'supportive' prenatal environment⁴⁹.

While GWAS-driven or biologically-informed polygenic scores have been used most frequently so far, it is also of note that we have recently published a cross-species approach, integrating data from a rat model of prenatal stress and human exposure to childhood maltreatment, which also identifies SNPs which show significant gene x environment interactions between exposure to stress and depressive symptoms⁵⁰.

Childhood Maltreatment

There is a growing body of evidence suggesting that childhood maltreatment is a key moderating factor in the development of adolescent psychopathology in the offspring of depressed mothers^{27,51,52}. A study conducted by our group⁵¹ has shown that children exposed to antenatal maternal depression are twice as likely to report having experienced childhood sexual or physical abuse or harsh parenting by the age of 11 years, while such link is not present in the case of postnatal depression. Furthermore, offspring who have been exposed to both antenatal depression and childhood maltreatment are almost 12-fold more likely to have a diagnosis of depressive disorder or conduct disorder in adolescence, but exposure to one or other of these factors in isolation does not lead to an increased risk. We have recently replicated these findings in a subsequent follow-up of the offspring at age 25²⁷. Interestingly, these studies also show that mothers suffering from antenatal depression are not more likely to be the sole perpetrators of maltreatment than healthy mothers; instead, the main perpetrators tend to be other close adults or even peers. Of note, a subsequent study conducted in the ALSPAC cohort has replicated the association between maternal antenatal depression and offspring exposure to childhood adversity⁵³.

Use of Antidepressants

Studying the risks and benefits of antidepressant use in pregnancy is very important, as this time represents a key point at which clinicians could intervene to optimise outcomes for unwell mothers and their babies. However, the issue is highly complex, due to the difficulties in disentangling the potentially toxic effects of any antidepressants that reach the fetus via the amniotic fluid⁵⁴, from the negative effects of untreated depression itself⁵⁵. Then, after birth, the picture becomes more complex still, as the effect of any antidepressants (or metabolites) transmitted to the baby through lactation must be weighed against the impact on the parenting behaviours of the mother due to her depressive symptoms.

The amount of research addressing the impact of antidepressants on a developing fetus or infant is substantial, especially for selective serotonin reuptake inhibitors (SSRIs), often the first-line treatment. SSRI use has increased during pregnancy in recent years, with up to 13% of pregnancies in both Europe and the US now involving exposure at some point^{56,57}. The potential adverse effects

of antidepressants on the risk of congenital malformations have been extensively reviewed before^{58,59}, and therefore will not be discussed here. In general, studies report that increased duration of antidepressant exposure is significantly associated with non-optimal obstetric outcomes, such as reduced gestational age, decreased birth weight, and increased risk of respiratory distress in the neonate⁶⁰. However, untreated depression also reduces gestational age and birth weight³⁵. The risk of reporting bias must also be considered, namely that a higher frequency of negative outcomes is reported by those taking antidepressants, as they are likely to be more vigilant.

In terms of behaviour, neonates that have been exposed to SSRIs during late gestation show symptoms affecting the central nervous system as well as the motor, respiratory and gastrointestinal systems⁶¹. This neonatal 'abstinence syndrome' is present in up to 30% of exposed babies⁶², and manifests as crying, tremor, reflux, jitteriness and sneezing, as well as sleep disturbances⁶³.

There is also some suggestion that drugs used to treat maternal depression may affect the neurobehavioural development^{64,65} and psychomotor development⁶⁶ of offspring, as well as slowing their reaching of major developmental milestones, such as sitting and walking unaided⁶⁷. However, other studies show these effects to be transient⁶⁸, and others do not find any association at all⁶⁹. One study found that antidepressant dose and duration does not predict cognitive or behavioural outcomes, and that the IQs of offspring exposed to depression with or without antidepressant treatment *in utero* are similar, although lower than those of the offspring of nondepressed mothers⁷⁰.

While attention often focuses on the potentially toxic effects of psychotropic medications on a developing fetus, it is also important to consider the negative impact of depression in women not taking their medication. A study by Cohen *et al.*⁷¹ has shown that 70% of depressed women who discontinue medication relapse during pregnancy, mostly in the first and second trimesters. It is also more likely that those who suffer from depression during pregnancy will continue to suffer from depression after birth⁷², which may affect the care quality that the infant receives, further impairing development. There is also a significantly higher risk of self-medication in depressed pregnant women²⁸, such as smoking or consuming alcohol and other legal and illegal drugs, and this also affects birth weight and other outcomes. Furthermore, despite concerns that psychotropic medications may be transmitted to the infant during breastfeeding, current evidence suggests that most medications show little or no risk to the infant⁷³.

Although this is a very difficult decision for every woman, on balance current evidence suggests that the consequences of untreated depression, especially for clinically-significant cases of depression, are more severe than those of antidepressants^{68,74–76}, especially considering all the evidence reviewed in this paper that testifies to the profound and enduring negative consequences of antenatal depression on the offspring⁷⁴. It is therefore vital that this risk of unmedicated depression is adequately evaluated before considering any detrimental effects of taking antidepressants.

Biological Mechanisms

There are many potential mechanisms which explain how an adverse intra-uterine environment can predispose to disorders later in life, including inflammation, epigenetic regulation, the development of brain structures, and placental mechanisms regulating the passage of stress hormones, such as cortisol⁷⁷, to the fetus. For postpartum psychosis, only few, very recent studies have started to evaluate the biological alterations in hormonal- and immune-mediated mechanisms, with biological samples usually acquired in the postpartum period. We will now review individual biological pathways, including specific genetic and epigenetic findings. For each pathway, we will first describe the available clinical evidence, and then we will present key preclinical evidence, where it adds further mechanistic insight.

Before we start this section, however, it is important to highlight the complexity involved in the interpretation of epigenetic findings. Indeed, recent research focusing on the intergenerational transmission of psychopathology, and on the associated maternal parenting styles, has proposed epigenetics as a key mechanism^{78,79}, with epigenetic changes occurring in the offspring in response to early life adversity⁸⁰ and abnormal parenting behaviours^{81,82}, and suggestions that these changes can be maintained over several generations by DNA methylation in the germline, although so far, pre-clinical evidence only supports this mechanism in the paternal germline⁸³. As Szyf and Bick⁸⁴ suggest, DNA methylation is capable of “embedding early life experiences in the genome”. However, it must be noted that epigenetic transmission does not need to occur only via the classical inheritance mechanisms. For example, if mother and offspring are exposed to similar environmental circumstances, they may develop similar epigenetic signatures independently of inheritance. Epigenetics may also be influenced by the effects of health-related circumstances on the growing fetus and developing child. For example, recent research shows that maternal obesity⁸⁵ can alter the methylation status of the infant, and maternal smoking can alter the methylation signature on the fetal side of the placenta⁸⁶. Indeed, even the mode of delivery can alter the infant’s methylation status, as measured in leucocytes⁸⁷. MicroRNAs are also considered a possible mediator of intergenerational effects on child outcomes, and indeed in the aforementioned paper from our group⁵⁰ we have identified 68 miRNAs (out of a total of 1218 miRNAs) that are significantly modulated by prenatal stress in the offspring rat hippocampus. Contributing to this complexity is also the notion that non-genetic inheritance can occur in relation to psychiatric conditions, where traits or characteristics are transmitted via molecular substrates, such as hormones and cytokines, travelling from mother to fetus through cord blood⁸⁸. Taken together, these lines of evidence demonstrate a need for caution when drawing ‘deterministic’ conclusions in the relationship between maternal behaviour and epigenetic changes in the offspring.

Hypothalamic-Pituitary-Adrenal Axis

The strongest body of evidence relating to perinatal psychiatry is that regarding the hypothalamic-pituitary-adrenal (HPA) axis, which not only has its own effects via different regulation of the glucocorticoid receptor or circulating cortisol levels, but also interacts with other major biological systems. For example, the interaction of estrogen and progesterone with the HPA axis is thought to

be crucial in the pathogenesis of perinatal depression, and has also been proposed as one of the pathophysiological mechanisms underlying the rapid onset of postpartum psychosis⁸⁹.

The Maternal HPA axis and its Effects on the Fetus

The accepted model postulates that exposure of the fetus to high levels of cortisol may result in subsequent effects on HPA axis, behaviour, and cognitive function of the offspring^{90–97}. For example, elevated levels of corticotrophin releasing hormone (CRH) and cortisol^{98–100} have been described in association with antenatal symptoms of depression. Moreover, studies have found associations between antenatal HPA axis and offspring HPA axis^{101–103}, or between antenatal HPA axis and infant behaviors or cognitive and motor development^{104–107}. Interestingly, by adolescence, data shows that exposure to maternal anxiety during pregnancy may reduce the cortisol awakening response in offspring¹⁰⁸, thus showing a complex and dynamic relationship between depression/anxiety-related HPA axis hyperactivity in pregnancy and changes in offspring HPA axis. The exact molecular mechanisms underlying these associations are however still unclear¹⁰⁹. Here we present some of these mechanisms.

Glucocorticoid Receptor and related genes

Glucocorticoid hormones, the final product of the HPA axis, play a crucial role during fetal development, in processes such as tissue maturation and cellular differentiation¹¹⁰. The glucocorticoid receptor (GR) is a central mediator in fetal programming and in the development and regulation of the HPA axis, and has thus been the focus of much research in recent years¹¹¹. There are many factors which affect the function and expression of the GR in the placenta, with one study showing that up to twelve different isoforms are present, whose expression can be dictated partly by fetal sex, as well as fetal size¹¹². Recently, attention has turned to the effects of stress on the epigenetic profile of the GR.

In humans, methylation of the GR gene in offspring is increased by parental psychopathology¹¹³ and early-life trauma¹¹⁴. However, it must be noted that, aside from a handful of studies looking at post-mortem brains^{115–117}, human studies usually analyse the epigenome of peripheral tissues (most often, blood), which may not represent tissue-specific epigenetic changes occurring in the brain. Indeed, there is some debate about how reliable peripheral measurements are when compared to methylation changes in the brain. For example, one study in mice shows similar methylation changes of the GR-related gene, the FK506 binding protein 5 (FKBP5), in the blood and hippocampus following treatment with high dose of corticosterone¹¹⁸. Another paper demonstrates that a functional polymorphism in the FKBP5 gene increases the risk of developing stress-related psychiatric disorders by allele-specific, childhood trauma-dependent DNA demethylation, leading to a global effect on the function of immune cells and brain areas associated with stress regulation¹¹⁹. However, the blood-brain correlations may be smaller when using genome-wide analyses rather than individual, hypothesis-driven genes, or in other brain areas. For example, one study correlating epigenetic signatures in the blood and temporal lobe biopsy tissues shows that only 8% of

methylation markers are consistent in the blood and brain, although this is still more than expected by chance¹²⁰.

Antenatal stress also affects the epigenetic profiles of GR (and GR-related genes), but the effects in mother and infant are distinct. For example, maternal antenatal experience of war¹²¹ or of intimate partner violence¹²² increase the GR methylation status analysed in blood samples from the newborn, even into adolescence¹²², while mother's epigenetic profile is unaffected. Moreover, pregnancy increases mRNA expression of the genes regulating the GR complex, FKPB5, BAG1, NCOA1 and PPID; however this increase is attenuated in women experiencing depression in pregnancy, indicating abnormal GR sensitivity¹²³. While there are no data in pregnancy from women who later develop postpartum psychosis, samples collected in the postpartum period from women with current symptoms of psychosis show that a dysregulation of the GR is also present in these women⁸⁹.

In addition to this clinical evidence, rodent models have shown that expression of the GR can be affected by the level of postpartum care, with the offspring of high licking-and-grooming mothers (a model of good maternal care) showing increased GR mRNA in the hippocampus and reduced HPA axis sensitivity to stress in adulthood¹²⁴. Evidence *in vitro* points to serotonin, and in particular to the 5-HT₇ receptor, as playing a role in increasing GR expression in this experimental condition¹²⁵, with enhanced serotonergic signalling increasing the expression of the transcription factor, nerve growth factors inducible protein A (NGFI-A), which then interacts directly with the GR promoter to increase its expression¹²⁶.

Interestingly, a study by Weaver *et al.*⁸¹ in rats has shown that licking and grooming not only alters GR expression in the offspring, but also changes the epigenome at the GR gene promoter. Neonates of mothers that are 'low licking-and-grooming' (i.e., showing low maternal care) have differences in hippocampal GR methylation which persist into adulthood and are associated with hypermethylation of the exon 1₇, hypoacetylation of histone H3 and reduced NGFI-A binding. This is thought to increase the stress response, by decreasing the GR-mediated negative feedback on the HPA axis.

Finally, our own *in vitro* work has shown that stress and glucocorticoids regulate neurogenesis in a human *in vitro* model using fetal hippocampal cells, as well as an animal model of prenatal stress¹²⁷, via stimulation of the GR. SGK1, a Serine/Threonine kinase which is implicated in neuronal function and cellular stress responses, mediates this cortisol-induced reduction in neurogenesis by phosphorylation of the GR. Expression of mRNA encoding SGK1 has also been shown to be elevated in the peripheral blood of depressed patients¹²⁸, suggesting that this molecular mechanism is relevant to the maintenance of psychopathology in adulthood.

Cortisol and 11-Beta-Hydroxysteroid Dehydrogenase Type 2

Epigenetic regulation of GR expression is not the only mechanism by which perinatal mental health can affect HPA axis function and regulation. As mentioned above, antenatal depression in humans is associated with high cortisol levels, a proportion of which is likely to be transported via the placenta to the fetus. To protect the fetus against some of these effects, the placenta forms a partial barrier which controls the proportion of maternal cortisol that reaches the fetus. Cortisol is converted by

the enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11 β -HSD-2) into the less active, cortisone; however antenatal stress, depression, and exposure to antidepressants, reduce the expression of this enzyme^{129,130}, potentially allowing the fetus to be exposed to the high cortisol levels in maternal circulation. In fact, it has been shown that low activity of placental 11 β -HSD2 correlates with lower fetal weight¹³¹ and with higher stress reactivity in the offspring¹²⁹. Consistent with this, in rodents, the offspring of 11 β -HSD2 knockout females are more prone to anxiety-related behaviours in later life¹³².

On a molecular level, inhibition of this enzyme in the placenta has been shown to affect GR expression in varying ways across the brain, with mRNA levels increased in the amygdala, but reduced in the hypothalamic paraventricular nucleus¹³³. Moreover, although the mechanism is unclear, sex differences are apparent in this protective mechanism, with male mouse fetuses showing superior protection to high levels of cortisol than females¹³⁴. It is possible that this is caused by functional and expression changes in 11 β -HSD2 due to differing methylation states of this enzyme, which are maintained in the offspring. In human preterm babies, lower levels of methylation of this enzyme are associated with a worse neurologic integrity and behavioural functioning¹³⁵.

Corticotrophin Releasing Hormone

In the first few weeks after childbirth, it is characteristic for women to show hyporeactivity of the HPA axis¹³⁶, as shown by blunting of the stress-related secretion of adrenocorticotrophic hormone (ACTH), a polypeptide tropic hormone. This hyporeactivity may be involved in explaining the sensitivity to mental health problems in the immediate weeks postpartum. In illustration of this, depressed mothers show more severe and long-lasting blunting of ACTH in response to corticotrophin releasing hormone (CRH) challenge at up to 12 weeks postpartum, in contrast to healthy women, for whom this blunting is less severe and has resolved by 12 weeks postpartum¹³⁶. A blunted ACTH response to CRH is considered a hallmark of major depression, and it is interpreted as a consequence of the increased production of hypothalamic CRH in these patients¹³⁷; therefore this evidence points toward an increased CRH drive also in perinatal depression (as mentioned above). In fact, one genetic association study found that a polymorphism in the CRH receptor 1 is associated with both pre- and post-natal depressive symptoms¹³⁸, although another group was subsequently unable to replicate these findings in the ALSPAC cohort¹³⁹.

Indeed, CRH has been considered as a potential pregnancy biomarker, predicting the development of depression later in pregnancy or postnatally. One particular focus has been the elevated CRH levels produced by the placenta, particularly when stimulated by glucocorticoids¹⁴⁰. CRH levels increase throughout pregnancy, via a positive feedback loop originating in the placenta⁶⁴, with levels in the plasma peaking during the third trimester¹⁴¹, before rapidly dropping after childbirth¹⁴². A relatively small study of antenatally depressed and non-depressed women has shown that elevated maternal blood CRH levels in the blood from weeks 24 to 37 predict a higher likelihood of depressive symptoms in the antenatal period¹⁰⁰; however this is conflicted by more recent research suggesting no such association¹⁴², and this association is also not found in the postpartum⁹⁸. In our recent paper, women with clinically-significant depression in pregnancy show raised diurnal cortisol secretion, raised evening cortisol and blunted cortisol awakening response together with an 8-day

shorter length of gestation; most relevant to this review, these women also have neonates with suboptimal neurobehavioral function and increased cortisol response to stress at one year of age, and maternal cortisol correlates with infant stress response, suggesting a mechanistic link¹⁴³. High levels of maternal CRH can also influence the neonatal behaviour of the offspring, such as impaired responses to novelty and heightened arousal¹⁴⁴.

Oxytocin

Oxytocin, the hormone commonly associated with childbirth, maternal attachment and lactation¹⁴⁵, is directly stimulated in offspring and mothers during attentive maternal behaviour. Indeed, mothers showing low maternal oxytocin levels during pregnancy are likely to show a lower frequency of positive bonding behaviour with their infants¹⁴⁶. This may be due to the apparent reciprocal link between oxytocin levels and mood in the perinatal period: antenatal depression is associated with low levels of oxytocin after birth¹⁴⁷, and low maternal oxytocin levels during pregnancy are significantly associated with increased risk of developing postnatal depression¹⁴⁸. Furthermore, there is some evidence to suggest that the genotype a woman carries at two loci for the oxytocin peptide, and one specific locus in the oxytocin receptor gene, can affect maternal interaction with her infant, and her experience of antenatal depression, respectively¹⁴⁹.

Administration of Intranasal Oxytocin

Given this link, studies have attempted to use oxytocin therapeutically, by administering a dose intranasally and measuring its effects on maternal bonding behaviours, but results have not been conclusive. Some of these studies have shown that a dose of intranasal oxytocin induces more protective behaviour in postnatally depressed mothers, who usually have a higher risk of less attentive behaviour toward their baby¹⁵⁰. Indeed, giving depressed mothers oxytocin increases their likelihood of rating the lowest pitch infant cries as urgent, when usually this type of cry is perceived as not urgent in healthy mothers; however, these oxytocin-treated mothers are also more likely to choose a harsh caregiving strategy¹⁵¹. It is therefore possible that (intranasal) oxytocin exacerbates a depressed mother's sensitivity to stress and the negative cognitive processes associated with the interpretation of infant cues. In addition, there is some evidence to suggest that intranasal oxytocin may negatively impact maternal mood¹⁵², perhaps unexpectedly, given the negative correlations between oxytocin levels in the perinatal period and mood disorders discussed above. Indeed, a recent study has shown that women exposed to synthetic oxytocin in the peripartum period have over 30% increased risk of developing postpartum depression or anxiety¹⁵³.

The interpretation of these studies must be cautious, however, as recent evidence indicates that the majority of the intranasal dose of oxytocin does not reach the cerebrospinal fluid, but instead remains in the periphery, thus acting on other organs such as the gastrointestinal, cardiovascular and reproductive systems¹⁵⁴. Recently it has been argued¹⁵⁴ that many earlier trials reporting positive effects on maternal behaviour were conducted using inaccurate methods to process blood

samples prior to oxytocin analysis, and recommend that plasma samples should be extracted to avoid matrix interference, prior to oxytocin measurement.

Regulation of Endogenous Oxytocin

Clinical studies have shown a robust association between mother and offspring levels of oxytocin, in sample types such as plasma, saliva and urine^{155,156}. One such study suggests that, mediated by level of maternal care experienced, both maternal and offspring levels of oxytocin predict children's social development and interaction with peers¹⁵⁷. Indeed, it is thought that well-adapted parenting is underpinned by oxytocin and the activation of reward-related brain mechanisms, while anxious parenting is associated with activation of stress-related regions of the brain¹⁵⁸. This is further demonstrated by studies showing that securely attached mothers show more activation of oxytocin-related regions of the brain, such as the hypothalamus and pituitary regions, on viewing their baby smiling or crying¹⁵⁹. In addition to this, women with a history of childhood abuse have decreased oxytocin concentrations in the cerebrospinal fluid¹⁶⁰.

Recent clinical research also suggests that oxytocin and its response is regulated by epigenetic modifications of the oxytocin receptor gene (*OXTR*). There is suggestive evidence of a correlation between childhood neglect or abuse and higher methylation of two sites of *OXTR*, in exon 3¹⁶¹. Another study¹⁶² also showed a significant association between postpartum depression and methylation at cg12695586 on *OXTR*. Furthermore, a higher number of stressful life events experienced by the mother during pregnancy, and elevated maternal cortisol levels, both reduce *OXTR* methylation in the cord blood¹⁶³, but increase *OXTR* methylation in offspring at birth¹⁶⁴. Finally, research in older people also indicates that methylation of the oxytocin receptor gene is dynamically regulated and influenced by environmental factors such as psychosocial stress¹⁶⁵. Taken together, this evidence suggests that the epigenetic profile of the infant can be programmed in utero by stressful maternal experience. Nevertheless, this evidence is not unequivocal. The pathway leading from prenatal adverse environment to altered *OXTR* methylation in humans is complicated, based on the definition of prenatal adverse environment. For example, two studies, both assessing cord blood, use different dimensions of psychopathology and psychosocial environment, and find different associations: one study found that increased number of life events in the two years up to middle gestation correlates with lower methylation (and hence, theoretically, higher expression)¹⁶³, while another study (in children with severe conduct disorder) shows that prenatal maternal psychopathology, criminal involvement and substance use are associated with higher *OXTR* methylation, but only in children who have conduct disorder and lower internalizing problems, perhaps reflecting genetic confounding rather than a causal relationship between in utero environment and cord blood methylation¹⁶⁴.

Animal models have been used to study the effects of oxytocin in the brain in more detail. Oxytocin release, similarly to in humans, can be stimulated by attentive maternal behaviour, such as licking and grooming in rats¹⁶⁶. Champagne and Meaney¹⁶⁷ have shown that 'high licking and grooming' lactating female rats have higher expression of oxytocin receptor in multiple brain areas, including the hypothalamus (medial preoptic area, MPOA) and the central nucleus of the amygdala; moreover, maternal stress reduces oxytocin receptor expression in these brain areas, which in turn is associated with reduced maternal care and is transmitted to offspring who, in adulthood, also show

low oxytocin receptor levels and poor maternal care quality. However, other brain areas are also involved in the effects of oxytocin on maternal behaviour. For example blockade of the oxytocin receptor in the medial pre-frontal cortex of postpartum female rats impairs maternal care behaviours and enhanced maternal aggression¹⁶⁸. In contrast, induction of the oxytocin receptor by estrogen in the ventromedial nucleus of the hypothalamus promotes female sexual behaviour, while induction in the central nucleus of the amygdala by dopamine gives rise to anxiolytic effects¹⁶⁹.

Taken together, this evidence points to multiple and complex effects of oxytocin beyond the simple regulation of maternal behaviour, depending on distinct signal transduction pathways and different regions of the brain, and tapping into a broad range of behavioural effects relevant to psychopathology.

Estrogen

Estrogen, a female sex hormone, is a potent regulator of a range of neural aspects such as mood and cognition¹⁴². Interestingly, a study in women with a history of postpartum depression reports that they show normal levels of circulating estrogen when euthymic, but abnormal sensitivity to childbirth-like estrogen withdrawal. Specifically, if these women are administered levels of estradiol and progesterone similar to those present during pregnancy, and then these hormones are withdrawn, mimicking the fall after childbirth, around 60% will develop mood symptoms, an effect which is absent in women with no history of postpartum depression¹⁷⁰. This notion further supported by data showing that women with postpartum depression have increased sensitivity to estrogen signalling in the third trimester of pregnancy, as shown by enrichment of estrogen-responsive mRNA transcripts' expression in the blood¹⁷¹. Women at risk of postpartum depression are also more sensitive to reprogramming of estrogen-based DNA methylation of genes associated with synaptic plasticity in the hippocampus¹⁷². Finally, a genome-wide linkage study has identified the hemicentin 1 gene locus, which contains multiple estrogen binding sites, to be associated with postpartum depressive symptoms⁴¹, although this finding was no longer significant after adjusting for multiple comparisons.

In addition to its independent actions, evidence emerging from preclinical models points to a pathway whereby the association between oxytocin, mood and maternal care behaviour discussed previously is also regulated by the presence of circulating estrogen and by epigenetic changes to the hypothalamic estrogen receptors⁷⁸. This could contribute to this lifelong pattern of abnormal response of the oxytocin system to changes in circulating levels of estrogen, and thus to abnormal maternal care behaviour. Interestingly, however, reduced maternal care seems to be associated with decreased sensitivity to estrogen signalling, due to increased methylation and thus reduced expression of the ER α in the hypothalamus. This contrasts with the aforementioned evidence of an increased estrogen sensitivity in the blood of women at risk of post-partum depression. This inconsistency may be underpinned by different epigenetic and functional regulation in the blood and in the brain.

A number of preclinical studies have confirmed the role of estrogen signalling in oxytocin regulation, including outcomes such as levels of maternal care. For example, in mouse models of anxiety-like behaviour, treatment with oxytocin has anxiolytic effects that are absent in ovariectomised animals,

unless they receive estradiol supplementation, possibly because estrogen may act by increasing oxytocin binding density in the lateral septum of the brain¹⁷³. Interestingly, these effects of estrogen on oxytocin regulation and activity seem to be specific for ER α , as this is essential for estrogen's induction of oxytocin receptor binding in the brain¹⁷⁴. Indeed, studies conducted in the 'licking and grooming' model shows that the aforementioned differences in oxytocin receptor expression in the MPOA between high and low LG females are estrogen dependent¹⁷⁵. A subsequent cross-fostering study confirmed an association between lower maternal care and decreased ER α expression in the MPOA, which is associated with higher levels of cytosine methylation across the ER α 1b promoter⁸², eventually leading to the aforementioned decreased estrogen sensitivity.

Neuroplasticity and Neurodevelopment

The significance of early neurodevelopment as a risk factor for mental health disorders is becoming increasingly apparent⁷⁷. Given that maternal mental illness during pregnancy has been shown to affect fetal neurodevelopment, it appears an important avenue of research when considering 'intergenerational transmission' of psychiatric disorders.

In the GUSTO (Growing up Towards Healthy Outcomes) study, a large and comprehensive birth cohort study in Singapore, prenatal maternal depression is associated with increased functional connectivity of the amygdala with the left temporal cortex and insula, as well as the medial orbitofrontal, bilateral anterior cingulate and ventromedial prefrontal cortices in the infant at 6 months¹⁷⁶; this is a pattern similar to that which is observed in adolescents and adults with major depressive disorder. However, a study from the same GUSTO cohort, but with a larger sample size, found that at age 4, prenatal maternal depressive symptoms were correlated with lower functional connectivity of the amygdala with other brain regions, although this was only observed in girls¹⁷⁷.

In another cohort, high levels of anxiety during pregnancy (particularly around week 19) is associated with a reduction in the density of grey matter in multiple regions of the brain of offspring aged 6-9, including the prefrontal cortex, premotor cortex, medial temporal lobe, postcentral gyrus and the cerebellum¹⁷⁸. This altered grey matter could explain the increased risk of psychopathology in the offspring. Reduced hippocampal volume has been observed also in children who have experienced trauma in childhood, and has been reported in patients remitted with major depression¹⁷⁹, so it likely contributes to resultant psychopathology in adulthood. Further, significant cortical thinning in the right frontal lobes has been shown in children exposed to maternal depression *in utero*¹⁸⁰.

As well as anatomical changes, there also appears to be parallel changes in maternal and infant neurotransmitter regulation, with lower levels of dopamine and serotonin reported in depressed mothers during pregnancy being mirrored in offspring urine samples taken within 24h of birth¹⁸¹. Interestingly, recent preclinical evidence also suggests that the reduction in maternal hippocampal neurogenesis caused by prenatal stress can be reversed using SSRI treatment¹⁸².

Of note, low levels of brain-derived neurotrophic factor (BDNF), which plays an important role in the development and maintenance of neural circuits, has been associated with vulnerability to the

development of various mental disorders in humans¹⁸³, and we have shown a concomitant reduction in GR and BDNF mRNA levels in the same adult depressed patients¹⁸⁴. While direct clinical evidence in the perinatal period is lacking, rodent models show that BDNF expression in the offspring can be affected by both maternal antenatal stress and early life stress. Specifically, neonates of a prenatally stressed rat show a reduction in BDNF in both the olfactory bulbs and in the hippocampus¹⁸⁵, while early maternal separation causes reduced levels of BDNF mRNA in the hippocampus of the offspring 9 days post-birth¹⁸⁶, and of BDNF protein in the medial prefrontal cortex (mPFC) in adulthood¹⁸⁷. This potential long-lasting effect of antenatal stress on BDNF expression found in preclinical models supports a role for BDNF, and its subsequent effect on synaptic plasticity, as a risk factor for intergenerational transmission of psychopathology.

Immune System

Recently, it has become apparent that the process of biological embedding of perinatal or childhood stress into adult psychopathology is also underpinned by changes in inflammatory pathways^{188,189}, as shown by studies in women suffering with postpartum depression¹⁹⁰ as well as children exposed to maltreatment¹⁹¹. In addition, recent data from our group in the aforementioned paper¹⁴³ have shown that women with antenatal depression have elevated levels of interleukin-6 (IL-6), tumour necrosis factor alpha (TNF α), IL-10 and vascular endothelial growth factor during pregnancy; moreover, as for cortisol, maternal inflammatory biomarkers correlate with infant stress response, suggesting a mechanistic link.

Depression is often manifested in conjunction with high levels of inflammatory biomarkers, especially in patients that are resistant to classic antidepressants^{192,193} and are exposed to maltreatment during childhood¹⁹⁴. Indeed, many studies now show that the inhibition of pro-inflammatory cytokines may improve low mood and, conversely, stimulation of the immune system may lower mood^{193,195,196}. Furthermore, a number of studies have shown that adults who experienced childhood trauma show elevated levels of many immune biomarkers, such as c-reactive-protein (CRP), TNF α and interleukins^{188,197–199}, an effect which can be seen in children as young as 12 years old¹⁹¹. There is also evidence that childhood exposure to medically-related inflammation, because of infections or medical disorders, is associated with a significantly increased risk of depression in adulthood²⁰⁰.

There is some evidence that altered immune activation is present in pregnancy and in the postpartum period in association with depressive symptoms^{201,202}. Indeed, one study has shown that regulatory T-cells are significantly increased in both the prenatal and postnatal period in mothers suffering depression¹⁹⁰. Another study has shown that experience of abuse may be the key moderator of this relationship, as experience of abuse and depression in pregnant adolescents predicts higher IL-6 concentration during pregnancy, but none such association in absence of exposure to abuse²⁰³. However, other studies investigating cytokine levels have shown that depressive symptoms during pregnancy are negatively correlated with cytokines such as IL-1 β , IL-7

and TNF α ^{204,205}. The results of these studies are partially confounded by the fact that, in general, they study variation of (self-related) depressive symptoms in large samples of pregnant women, rather than clinically-significant cases of antenatal depression. There is also evidence of an association between antenatal inflammation and behavioural outcomes in offspring²⁰⁶, suggesting that maternal inflammation may be relevant to some of the transgenerational outcomes observed in offspring. There is also evidence of an association between antenatal inflammation and behavioral outcomes in offspring²⁰⁶, suggesting that maternal inflammation may be relevant to some of the transgenerational outcomes observed in offspring.

Higher levels of pro-inflammatory cytokines have also been reported in individuals with psychoses suggesting that inflammatory pathways may also underpin psychotic symptoms^{207,208}, and in fact, a dysregulation of the immune system and glucocorticoid response has also been reported in postpartum psychosis⁸⁹. Specifically, compared to postpartum women with no psychosis, those who develop postpartum psychosis have been found to have higher serum IL-1 β levels and T-cell numbers, together with an upregulation of genes involved in the immune system⁸⁹. In addition, women with postpartum psychosis show a decreased glucocorticoid receptor α/β gene expression in monocytes, which strongly correlates with the immune activation²⁰⁹. This points to the presence of alterations in both immune and neuroendocrine systems in postpartum psychosis that are similar to that observed in mood disorders and other psychoses.

One possible molecular mechanism by which immune dysregulation is associated with psychopathology is through abnormal serotonin metabolism²¹⁰. Indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) are the two major enzymes involved in the metabolism of tryptophan, the serotonin precursor. IDO is directly activated by pro-inflammatory signals, such as TNF α and IFN γ , while TDO is activated by cortisol^{211,212}. Of particular interest in pregnancy, TDO is also inhibited by estrogens and progesterone, a potential mechanism for the putative antidepressant effects of these hormones during pregnancy²¹³.

There is evidence that differences in the accumulation of neurotoxic kynurenine metabolites may precipitate the psychiatric symptoms in the perinatal period^{210,214}. Indeed, a recent study²⁰² has shown that both cortisol and the ratio between pro- and anti-inflammatory cytokines are elevated postpartum in mothers with depression (although TNF α levels are significantly lower in depressed mothers), confirming the hypothesis that a combined increase in activators of both IDO and TDO could play an important role in serotonin availability. This mechanism may also participate to the association between antenatal depression and low fetal birth weight²¹³, since tryptophan availability is vital for protein synthesis in fetal development.

It is possible to speculate that epigenetic changes to the genes encoding immune molecules, as a result of perinatal or childhood adversity²¹⁵, provokes long-term immune dysregulation, which then, in addition to the high cortisol levels associated with perinatal depression, may deplete serotonin availability in the offspring, thus maintaining the risk for depression in adulthood²¹³. Indeed, we have recently shown that adult offspring of mothers who were depressed in pregnancy show, at age 25, increased inflammatory levels, as measured by blood CRP, even in the absence of depression; this confirms the notion that perinatal events, and antenatal depression in particular, induce long-term activation of the immune system in the offspring²¹⁶.

Of note in this context is also the possibility of using omega-3 fatty acids, a potentially anti-inflammatory treatment, as a safe antidepressant during pregnancy. In our trial using this approach in women with a diagnosis of major depressive disorder in pregnancy, we found that omega-3 supplementation reduces depressive symptoms²¹⁷. Subsequent studies that have investigated the prophylactic effects of omega-3 in women 'at risk' of depression in pregnancy or postpartum, however, have not found beneficial effects^{218,219}, suggesting that the effects are most evident in more severe forms of antenatal depression. Our *in vitro* work has also recently shown that omega-3 fatty acids, like some antidepressants, reduce activation of the IDO pathways²²⁰.

A lot of research in animal models has used biological immune challenges, such as lipopolysaccharide, during pregnancy, to investigate the effects of a hyperactive maternal immune system on the developing fetus^{221–223}. However, for this review we focus on psychological or stress challenges, as they are more relevant to prenatal psychopathology. Recent work²²⁴ has studied the effects of psychological stress in late gestation on postpartum neuroimmune function. After exposure to a forced swim test in late gestation, region-specific neuroimmune changes were observed in the mother's brain postpartum, such as a reduction of IL-1 β in the mPFC and an increased microglia density in the hippocampus. Increased expression of genes associated with the immune system can also be seen in the placenta following prenatal stress, particularly where the fetus is male, as shown by higher mRNA levels of IL-1 β ²²⁵.

Interestingly, changes in the expression of immune biomarkers can be seen also in the offspring following prenatal stress. For example, studies have reported increased levels of IL-1 β mRNA in the hippocampus of both male²²⁶ and female²²⁷ offspring in adulthood (4 months). Interestingly, another study has shown increased inflammation in adult rats aged 6 months, with higher mRNA expression of interferon gamma (IFN γ) as a result of prenatal stress; however these alterations were undetectable in the rats when they were just 7 weeks old²²⁸. Recent evidence both *in vitro*²²⁹ and *in vivo*²³⁰ suggests that these long-lasting inflammatory alterations in adult rodents exposed to prenatal stress may be associated with malfunctions in fractalkine signalling, a chemokine important for the migration, differentiation and proliferation of neuronal and glial cells.

Concluding Remarks

There is a wealth of research studying the effects of perinatal psychiatry on offspring outcomes, with at least three, parallel molecular pathways operating across the two generations: oxytocin, glucocorticoids, and inflammation (see figure 1). However, the methods of research are challenging, as experimental studies cannot capture the heterogeneity and complexity of the clinical conditions, and the clinical samples often present many contributing factors and outcomes that occur in parallel. For example, perinatal depression is often suffered in conjunction with perinatal anxiety or high current stress levels, and often in women with a previous history of mental illness and exposure to life adversity in childhood. In terms of outcome, and especially the increased risk of psychopathology in the offspring, it is important to note that the offspring of mothers suffering with depression are not only exposed to ‘the environment’ (for example, abnormal HPA axis function *in utero* or poor attachment and parenting behaviours postpartum), but are also likely to have a genetic predisposition to psychopathology, which may partly be related to the same molecular mechanisms²³¹.

Future research should investigate fetal programming in humans by combining in-depth clinical assessments with sophisticated molecular investigations, in cohorts of mothers and babies assessed prospectively. Ultimately, the ambition is that of elucidating the mechanisms by which the regulation of the maternal molecular systems discussed above can be ‘transmitted’ to the fetus and eventually culminate in psychopathology in the offspring during later life, and of using this understanding to predict, prevent or treat perinatal psychopathology, thus breaking the vicious intergenerational cycle.

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References

- 1 Bonari L, Pinto N, Ahn E, Einarson A, Steiner M, Koren G. Perinatal risks of untreated depression during pregnancy. *Can J Psychiatry* 2004; **49**: 726–35.
- 2 Biaggi A, Conroy S, Pawlby S, Pariante CM. Identifying the women at risk of antenatal anxiety and depression: A systematic review. *J Affect Disord* 2016; **191**: 62–77.
- 3 Stein A, Pearson RM, Goodman SH, Rapa E, Rahman A, McCallum M *et al*. Effects of perinatal mental disorders on the fetus and child. 2014.
- 4 Murray L, Kempton C, Woolgar M, Hooper R. Depressed mothers' speech to their infants and its relation to infant gender and cognitive development. *J Child Psychol Psychiatry* 1993; **34**: 1083–101.
- 5 Sit D, Rothschild AJ, Wisner KL. A review of postpartum psychosis. *J Womens Health (Larchmt)* 2006; **15**: 352–68.
- 6 Feldman R, Granat A, Pariente C, Kanety H, Kuint J, Gilboa-Schechtman E. Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. *J Am Acad Child Adolesc Psychiatry* 2009; **48**: 919–927.
- 7 Murray L. The Impact of Postnatal Depression on Infant Development. *J Child Psychol Psychiatry* 1992; **33**: 543–561.
- 8 Leis JA, Heron J, Stuart EA, Mendelson T. Associations between maternal mental health and child emotional and behavioral problems: Does prenatal mental health matter? *J Abnorm Child Psychol* 2014; **42**: 161–171.
- 9 Evans J, Melotti R, Heron J, Ramchandani P, Wiles N, Murray L *et al*. The timing of maternal depressive symptoms and child cognitive development: a longitudinal study. *J Child Psychol Psychiatry* 2012; **53**: 632–640.
- 10 Pearson RM, Evans J, Kounali D, Lewis G, Heron J, Ramchandani PG *et al*. Maternal depression during pregnancy and the postnatal period: risks and possible mechanisms for offspring depression at age 18 years. *JAMA psychiatry* 2013; **70**: 1312–9.
- 11 Barker ED, Jaffee SR, Uher R, Maughan B. The contribution of prenatal and postnatal maternal anxiety and depression to child maladjustment. *Depress Anxiety* 2011; **28**: 696–702.
- 12 Hanington L, Heron J, Stein A, Ramchandani P. Parental depression and child outcomes - is marital conflict the missing link? *Child Care Health Dev* 2012; **38**: 520–529.
- 13 Letourneau NL, Tramonte L, Willms JD. Maternal Depression, Family Functioning and Children's Longitudinal Development. *J Pediatr Nurs* 2013; **28**: 223–234.
- 14 Naicker K, Wickham M, Colman I, Swartz M, Hemmingsson T. Timing of First Exposure to Maternal Depression and Adolescent Emotional Disorder in a National Canadian Cohort. *PLoS One* 2012; **7**: e33422.
- 15 Galéra C, Côté SM, Bouvard MP, Pingault J-B, Melchior M, Michel G *et al*. Early Risk Factors for Hyperactivity-Impulsivity and Inattention Trajectories From Age 17 Months to 8 Years. *Arch Gen Psychiatry* 2011; **68**: 1267.
- 16 Velders FP, Dieleman G, Henrichs J, Jaddoe VW V., Hofman A, Verhulst FC *et al*. Prenatal and

- postnatal psychological symptoms of parents and family functioning: the impact on child emotional and behavioural problems. *Eur Child Adolesc Psychiatry* 2011; **20**: 341–350.
- 17 Van Batenburg-Eddes T, Brion MJJ, Henrichs J, Jaddoe VVW V, Hofman A, Verhulst FCC *et al.* Parental depressive and anxiety symptoms during pregnancy and attention problems in children: A cross-cohort consistency study. *J Child Psychol Psychiatry Allied Discip* 2013; **54**: 591–600.
 - 18 Tharner A, Luijk MPCM, van IJzendoorn MH, Bakermans-Kranenburg MJ, Jaddoe VVW, Hofman A *et al.* Maternal lifetime history of depression and depressive symptoms in the prenatal and early postnatal period do not predict infant–mother attachment quality in a large, population-based Dutch cohort study. *Attach Hum Dev* 2012; **14**: 63–81.
 - 19 Verbeek T, Bockting CLH, van Pampus MG, Ormel J, Meijer JL, Hartman CA *et al.* Postpartum depression predicts offspring mental health problems in adolescence independently of parental lifetime psychopathology. *J Affect Disord* 2012; **136**: 948–954.
 - 20 Kersten-Alvarez LE, Hosman CMH, Riksen-Walraven JM, van Doesum KTM, Smeekens S, Hoefnagels C. Early School Outcomes for Children of Postpartum Depressed Mothers: Comparison with a Community Sample. *Child Psychiatry Hum Dev* 2012; **43**: 201–218.
 - 21 Hartley C, Pretorius K, Mohamed A, Laughton B, Madhi S, Cotton MF *et al.* Maternal postpartum depression and infant social withdrawal among human immunodeficiency virus (HIV) positive mother–infant dyads. *Psychol Health Med* 2010; **15**: 278–287.
 - 22 Noorlander Y, Bergink V, Van Den Berg MP. Perceived and observed mother-child interaction at time of hospitalization and release in postpartum depression and psychosis. *Arch Womens Ment Health* 2008; **11**: 49–56.
 - 23 Hornstein C, Trautmann-Villalba P, Hohm E, Rave E, Wortmann-Fleischer S, Schwarz M. Maternal bond and mother-child interaction in severe postpartum psychiatric disorders: is there a link? *Arch Womens Ment Health* 2006; **9**: 279–84.
 - 24 Chandra PS, Bhargavaraman RP, Raghunandan VNGP, Shaligram D. Delusions related to infant and their association with mother-infant interactions in postpartum psychotic disorders. *Arch Womens Ment Health* 2006; **9**: 285–8.
 - 25 Pawlby S, Hay DF, Sharp D, Waters CS, O’Keane V. Antenatal depression predicts depression in adolescent offspring: Prospective longitudinal community-based study. *J Affect Disord* 2009; **113**: 236–243.
 - 26 O KJ, Glover V, Barker ED, O TG. The persisting effect of maternal mood in pregnancy on childhood psychopathology. 2017. doi:10.1017/S0954579414000029.
 - 27 Plant DT, Pariante CM, Sharp D, Pawlby S. Maternal depression during pregnancy and offspring depression in adulthood: Role of child maltreatment. *Br J Psychiatry* 2015; **207**: 213–220.
 - 28 Hay DF, Pawlby S, Waters CS, Sharp D. Antepartum and postpartum exposure to maternal depression: different effects on different adolescent outcomes. *J Child Psychol Psychiatry* 2008; **49**: 1079–88.
 - 29 Capron LE, Glover V, Pearson RM, Evans J, O’Connor TG, Stein A *et al.* Associations of maternal and paternal antenatal mood with offspring anxiety disorder at age 18 years. *J Affect Disord* 2015; **187**: 20–6.

- 30 Munhoz TN, Santos IS, Barros AJD, Anselmi L, Barros FC, Matijasevich A. Perinatal and postnatal risk factors for disruptive mood dysregulation disorder at age 11: 2004 Pelotas Birth Cohort Study. *J Affect Disord* 2017; **215**: 263–268.
- 31 Lovejoy MC, Graczyk PA, O'Hare E, Neuman G. Maternal depression and parenting behavior: a meta-analytic review. *Clin Psychol Rev* 2000; **20**: 561–92.
- 32 Jaser SS, Fear JM, Reeslund KL, Champion JE, Reising MM, Compas BE. Maternal sadness and adolescents' responses to stress in offspring of mothers with and without a history of depression. *J Clin Child Adolesc Psychol* 2008; **37**: 736–46.
- 33 Brennan PA, Le Brocque R, Hammen C. Maternal depression, parent-child relationships, and resilient outcomes in adolescence. *J Am Acad Child Adolesc Psychiatry* 2003; **42**: 1469–77.
- 34 Nosarti C, Reichenberg A, Murray RM, Cnattingius S, Lambe MP, Yin L *et al*. Preterm birth and psychiatric disorders in young adult life. *Arch Gen Psychiatry* 2012; **69**: E1-8.
- 35 Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch Gen Psychiatry* 2010; **67**: 1012–24.
- 36 Jarde A, Morais M, Kingston D, Giallo R, MacQueen GM, Giglia L *et al*. Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression. *JAMA Psychiatry* 2016; **73**: 826.
- 37 O'Donnell KJ, Meaney MJ. Fetal Origins of Mental Health: The Developmental Origins of Health and Disease Hypothesis. *Am J Psychiatry* 2017; **174**: 319–328.
- 38 Kendler KS, Gatz M, Gardner CO, Pedersen NL. A Swedish National Twin Study of Lifetime Major Depression. *Am J Psychiatry* 2006; **163**: 109–114.
- 39 Reising MM, Watson KH, Hardcastle EJ, Merchant MJ, Roberts L, Forehand R *et al*. Parental Depression and Economic Disadvantage: The Role of Parenting in Associations with Internalizing and Externalizing Symptoms in Children and Adolescents. *J Child Fam Stud* 2013; **22**. doi:10.1007/s10826-012-9582-4.
- 40 Couto TCE, Brancaglioni MYM, Alvim-Soares A, Moreira L, Garcia FD, Nicolato R *et al*. Postpartum depression: A systematic review of the genetics involved. *World J psychiatry* 2015; **5**: 103–11.
- 41 Mahon PB, Payne JL, MacKinnon DF, Mondimore FM, Goes FS, Schweizer B *et al*. Genome-Wide Linkage and Follow-Up Association Study of Postpartum Mood Symptoms. *Am J Psychiatry* 2009; **166**: 1229–1237.
- 42 Viktorin A, Meltzer-Brody S, Kuja-Halkola R, Sullivan PF, Landén M, Lichtenstein P *et al*. Heritability of Perinatal Depression and Genetic Overlap With Nonperinatal Depression. *Am J Psychiatry* 2016; **173**: 158–165.
- 43 Rice F, Harold GT, Boivin J, van den Bree M, Hay DF, Thapar A. The links between prenatal stress and offspring development and psychopathology: disentangling environmental and inherited influences. *Psychol Med* 2010; **40**: 335–45.
- 44 Nomura Y, Wickramaratne PJ, Pilowsky DJ, Newcorn JH, Bruder-Costello B, Davey C *et al*. Low birth weight and risk of affective disorders and selected medical illness in offspring at high and low risk for depression. *Compr Psychiatry* 2007; **48**: 470–8.

- 45 Pluess M, Velders FP, Belsky J, van IJzendoorn MH, Bakermans-Kranenburg MJ, Jaddoe VW V *et al.* Serotonin transporter polymorphism moderates effects of prenatal maternal anxiety on infant negative emotionality. *Biol Psychiatry* 2011; **69**: 520–5.
- 46 Wazana A, Moss E, Jolicoeur-Martineau A, Graffi J, Tsabari G, Lecompte V *et al.* The interplay of birth weight, dopamine receptor D4 gene (DRD4), and early maternal care in the prediction of disorganized attachment at 36 months of age. *Dev Psychopathol* 2015; **27**: 1145–1161.
- 47 Qiu A, Shen M, Buss C, Chong Y-S, Kwek K, Saw S-M *et al.* Effects of Antenatal Maternal Depressive Symptoms and Socio-Economic Status on Neonatal Brain Development are Modulated by Genetic Risk. *Cereb Cortex* 2017; **27**: 3080–3092.
- 48 Silveira PP, Pokhvisneva I, Parent C, Cai S, Rema ASS, Broekman BFP *et al.* Cumulative prenatal exposure to adversity reveals associations with a broad range of neurodevelopmental outcomes that are moderated by a novel, biologically informed polygenic score based on the serotonin transporter solute carrier family C6, member 4 (SLC6A4) gene expression. *Dev Psychopathol* 2017; **29**: 1601–1617.
- 49 Belsky J, Pokhvisneva I, Rema ASS, Broekman BFP, Pluess M, O'Donnell KJ *et al.* Polygenic differential susceptibility to prenatal adversity. *Dev Psychopathol* 2018; : 1–3.
- 50 Cattaneo A, Cattane N, Malpighi C, Czamara D, Suarez A, Mariani N *et al.* FoxO1, A2M, and TGF- β 1: three novel genes predicting depression in gene X environment interactions are identified using cross-species and cross-tissues transcriptomic and miRNomic analyses. *Mol Psychiatry* 2018; : 1.
- 51 Pawlby S, Hay D, Sharp D, Cerith S W, Pariante CM. Antenatal depression and offspring psychopathology: The influence of childhood maltreatment. *Br J Psychiatry* 2011; **199**: 106–112.
- 52 Plant DT, Barker ED, Waters CS, Pawlby S, Pariante CM. Intergenerational transmission of maltreatment and psychopathology: the role of antenatal depression. *Psychol Med* 2013; **43**: 519–528.
- 53 Lereya ST, Wolke D. Prenatal family adversity and maternal mental health and vulnerability to peer victimisation at school. *J Child Psychol Psychiatry* 2013; **54**: 644–652.
- 54 Paulzen M, Goecke TW, Stickeler E, Gründer G, Schoretsanis G. Sertraline in pregnancy – Therapeutic drug monitoring in maternal blood, amniotic fluid and cord blood. *J Affect Disord* 2017; **212**: 1–6.
- 55 Koren G. SSRIs in pregnancy--are they safe? *Pediatr Res* 2002; **51**: 424–5.
- 56 Bakker MK, Kölling P, van den Berg PB, de Walle HEK, de Jong van den Berg LTW. Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. *Br J Clin Pharmacol* 2008; **65**: 600–6.
- 57 Cooper WO, Willy ME, Pont SJ, Ray WA, Pirraglia PA, Stafford RS *et al.* Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol* 2007; **196**: 544.e1–544.e5.
- 58 Mcallister-Williams RH, Baldwin DS, Cantwell R. British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. *J Psychopharmacol Hampsh Perinat Ment Heal Serv* 2017. doi:10.1177/0269881117699361.

- 59 Grigoriadis S, VonderPorten EH, Mamisashvili L, Tomlinson G, Dennis C-L, Koren G *et al.* The impact of maternal depression during pregnancy on perinatal outcomes: a systematic review and meta-analysis. *J Clin Psychiatry* 2013; **74**: e321-41.
- 60 Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Effects of timing and duration of gestational exposure to serotonin reuptake inhibitor antidepressants: population-based study. *Br J Psychiatry* 2008; **192**: 338–343.
- 61 Moses-Kolko EL, Bogen D, Perel J, Bregar A, Uhl K, Levin B *et al.* Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA* 2005; **293**: 2372–83.
- 62 Levinson-Castiel R, Merlob P, Linder N, Sirota L, Klinger G. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. *Arch Pediatr Adolesc Med* 2006; **160**: 173–6.
- 63 Galbally M, Lewis AJ, Lum J, Buist A. Serotonin discontinuation syndrome following in utero exposure to antidepressant medication: prospective controlled study. *Aust N Z J Psychiatry* 2009; **43**: 846–54.
- 64 Monk C, Fitelson EM, Werner E. Mood disorders and their pharmacological treatment during pregnancy: Is the future child affected? *Pediatr. Res.* 2011; **69**: 3R–10R.
- 65 Van den Bergh BRH, Mulder EJM, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neurosci Biobehav Rev* 2005; **29**: 237–58.
- 66 Casper RC, Fleisher BE, Lee-Ancas JC, Gilles A, Gaylor E, DeBattista A *et al.* Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *J Pediatr* 2003; **142**: 402–8.
- 67 Pedersen LH, Henriksen TB, Olsen J. Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age. *Pediatrics* 2010; **125**: e600-8.
- 68 Previti G, Pawlby S, Chowdhury S, Aguglia E, Pariante CM. Neurodevelopmental outcome for offspring of women treated for antenatal depression: a systematic review. *Arch Womens Ment Health* 2014; **17**: 471–83.
- 69 Austin M-P, Karatas JC, Mishra P, Christl B, Kennedy D, Oei J. Infant neurodevelopment following *in utero* exposure to antidepressant medication. *Acta Paediatr* 2013; **102**: n/a-n/a.
- 70 Nulman I, Koren G, Rovet J, Barrera M, Pulver A, Streiner D *et al.* Neurodevelopment of Children Following Prenatal Exposure to Venlafaxine, Selective Serotonin Reuptake Inhibitors, or Untreated Maternal Depression. *Am J Psychiatry* 2012; **169**: 1165–1174.
- 71 Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC *et al.* Relapse of Major Depression During Pregnancy in Women Who Maintain or Discontinue Antidepressant Treatment. *JAMA* 2006; **295**: 499.
- 72 Robertson E, Grace S, Wallington T, Stewart DE. Antenatal risk factors for postpartum depression: a synthesis of recent literature. *Gen Hosp Psychiatry* 2004; **26**: 289–295.
- 73 Payne JL. Psychopharmacology in Pregnancy and Breastfeeding. *Psychiatr Clin North Am* 2017; **40**: 217–238.

- 74 Pariante CM. Depression and antidepressants in pregnancy: Molecular and psychosocial mechanisms affecting offspring's physical and mental health. 2015.
- 75 Ornoy A. Neurobehavioral risks of SSRIs in pregnancy: comparing human and animal data. *Reprod Toxicol* 2017. doi:10.1016/j.reprotox.2017.05.003.
- 76 Latendresse G, Elmore C, Deneris A. Selective Serotonin Reuptake Inhibitors as First-Line Antidepressant Therapy for Perinatal Depression. *J Midwifery Womens Health* 2017. doi:10.1111/jmwh.12607.
- 77 Newman L, Judd F, Olsson CA, Castle D, Bousman C, Sheehan P *et al.* Early origins of mental disorder - risk factors in the perinatal and infant period. *BMC Psychiatry* 2016; **16**: 270.
- 78 Champagne FA. Epigenetic mechanisms and the transgenerational effects of maternal care. *Front Neuroendocrinol* 2008; **29**: 386–97.
- 79 Bowers ME, Yehuda R. Intergenerational Transmission of Stress in Humans. *Neuropsychopharmacology* 2016; **41**: 232–244.
- 80 Essex MJ, Boyce WT, Hertzman C, Lam LL, Armstrong JM, Neumann SMA *et al.* Epigenetic vestiges of early developmental adversity: childhood stress exposure and DNA methylation in adolescence. *Child Dev*; **84**: 58–75.
- 81 Weaver ICG, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR *et al.* Epigenetic programming by maternal behavior. *Nat Neurosci* 2004; **7**: 847–854.
- 82 Champagne FA, Weaver ICG, Diorio J, Dymov S, Szyf M, Meaney MJ. Maternal care associated with methylation of the estrogen receptor- α 1b promoter and estrogen receptor- α expression in the medial preoptic area of female offspring. *Endocrinology* 2006; **147**: 2909–15.
- 83 Franklin TB, Russig H, Weiss IC, Gräff J, Linder N, Michalon A *et al.* Epigenetic transmission of the impact of early stress across generations. *Biol Psychiatry* 2010; **68**: 408–15.
- 84 Szyf M, Bick J. DNA methylation: a mechanism for embedding early life experiences in the genome. *Child Dev* 2013; **84**: 49–57.
- 85 Sureshchandra S, Wilson RM, Rais M, Marshall NE, Purnell JQ, Thornburg KL *et al.* Maternal Pregravid Obesity Remodels the DNA Methylation Landscape of Cord Blood Monocytes Disrupting Their Inflammatory Program. *J Immunol* 2017; **199**: 2729–2744.
- 86 van Otterdijk SD, Binder AM, Michels KB. Locus-specific DNA methylation in the placenta is associated with levels of pro-inflammatory proteins in cord blood and they are both independently affected by maternal smoking during pregnancy. *Epigenetics* 2017; : 00–00.
- 87 Schlinzig T, Johansson S, Gunnar A, Ekström T, Norman M. Epigenetic modulation at birth - altered DNA-methylation in white blood cells after Caesarean section. *Acta Paediatr* 2009; **98**: 1096–1099.
- 88 Toth M. Mechanisms of Non-Genetic Inheritance and Psychiatric Disorders. *Neuropsychopharmacology* 2015; **40**: 129–140.
- 89 Bergink V, Gibney SM, Drexhage HA. Autoimmunity, inflammation, and psychosis: A search for peripheral markers. 2014.
- 90 Seckl JR. Glucocorticoid programming of the fetus; adult phenotypes and molecular

- mechanisms. *Mol Cell Endocrinol* 2001; **185**: 61–71.
- 91 Seckl JR. Prenatal glucocorticoids and long-term programming. *Eur J Endocrinol* 2004; **151 Suppl 3**: U49–62.
 - 92 Seckl JR, Holmes MC. Mechanisms of Disease: glucocorticoids, their placental metabolism and fetal ‘programming’ of adult pathophysiology. *Nat Clin Pract Endocrinol Metab* 2007; **3**: 479–488.
 - 93 Cottrell EC, Seckl J. Prenatal stress, glucocorticoids and the programming of adult disease. *Front Behav Neurosci* 2009; **3**: 19.
 - 94 Reynolds RM. Glucocorticoid excess and the developmental origins of disease: Two decades of testing the hypothesis – 2012 Curt Richter Award Winner. *Psychoneuroendocrinology* 2013; **38**: 1–11.
 - 95 Moisiadis VG, Matthews SG. Glucocorticoids and fetal programming part 1: outcomes. *Nat Rev Endocrinol* 2014; **10**: 391–402.
 - 96 Moisiadis VG, Matthews SG. Glucocorticoids and fetal programming part 2: mechanisms. *Nat Rev Endocrinol* 2014; **10**: 403–411.
 - 97 Glover V. Prenatal Stress and Its Effects on the Fetus and the Child: Possible Underlying Biological Mechanisms. In: *Advances in neurobiology*. 2015, pp 269–283.
 - 98 Rich-Edwards JW, Mohllajee AP, Kleinman K, Hacker MR, Majzoub J, Wright RJ *et al*. Elevated midpregnancy corticotropin-releasing hormone is associated with prenatal, but not postpartum, maternal depression. *J Clin Endocrinol Metab* 2008; **93**: 1946–51.
 - 99 O’Connor TG, Tang W, Gilchrist MA, Moynihan JA, Pressman EK, Blackmore ER. Diurnal cortisol patterns and psychiatric symptoms in pregnancy: Short-term longitudinal study. *Biol Psychol* 2014; **96**: 35–41.
 - 100 O’Keane V, Lightman S, Marsh M, Pawlby S, Papadopoulos AS, Taylor A *et al*. Increased pituitary-adrenal activation and shortened gestation in a sample of depressed pregnant women: a pilot study. *J Affect Disord* 2011; **130**: 300–5.
 - 101 Gutteling BM, de Weerth C, Buitelaar JK. Short Communication Maternal Prenatal Stress and 4–6 Year Old Children’s Salivary Cortisol Concentrations Pre- and Post-vaccination. *Stress* 2004; **7**: 257–260.
 - 102 Gutteling BM, Weerth C de, Buitelaar JK. Prenatal stress and children’s cortisol reaction to the first day of school. *Psychoneuroendocrinology* 2005; **30**: 541–549.
 - 103 O’Connor TG, Bergman K, Sarkar P, Glover V. Prenatal cortisol exposure predicts infant cortisol response to acute stress. *Dev Psychobiol* 2013; **55**: 145–155.
 - 104 Huizink AC, Robles de Medina PG, Mulder EJH, Visser GHA, Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. *J Child Psychol Psychiatry* 2003; **44**: 810–8.
 - 105 de Weerth C, van Hees Y, Buitelaar JK. Prenatal maternal cortisol levels and infant behavior during the first 5 months. *Early Hum Dev* 2003; **74**: 139–51.
 - 106 DAVIS EP, Glynn LM, SCHETTER CD, Hobel C, CHICZ-DEMET A, SANDMAN CA. Prenatal Exposure to Maternal Depression and Cortisol Influences Infant Temperament. *J Am Acad*

- Child Adolesc Psychiatry* 2007; **46**: 737–746.
- 107 Davis EP, Sandman CA. The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. *Child Dev* 2010; **81**: 131–48.
 - 108 O'Donnell KJ, Glover V, Jenkins J, Browne D, Ben-Shlomo Y, Golding J *et al*. Prenatal maternal mood is associated with altered diurnal cortisol in adolescence. *Psychoneuroendocrinology* 2013; **38**: 1630–8.
 - 109 Weinstock M. The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain Behav Immun* 2005; **19**: 296–308.
 - 110 Cottrell EC, Seckl JR. Prenatal stress, glucocorticoids and the programming of adult disease. *Front Behav Neurosci* 2009; **3**: 19.
 - 111 Pariante CM. Depression during pregnancy: molecular regulations of mothers' and children's behaviour. *Biochem Soc Trans* 2014; **42**: 582–6.
 - 112 Saif Z, Hodyl NA, Hobbs E, Tuck AR, Butler MS, Osei-Kumah A *et al*. The human placenta expresses multiple glucocorticoid receptor isoforms that are altered by fetal sex, growth restriction and maternal asthma. *Placenta* 2014; **35**: 260–268.
 - 113 Turecki G, Meaney MJ. Effects of the Social Environment and Stress on Glucocorticoid Receptor Gene Methylation: A Systematic Review. *Biol Psychiatry* 2016; **79**: 87–96.
 - 114 Smart C, Strathdee G, Watson S, Murgatroyd C, McAllister-Williams RH. Early life trauma, depression and the glucocorticoid receptor gene – an epigenetic perspective. *Psychol Med* 2015; **45**: 3393–3410.
 - 115 Chen ES, Ernst C, Turecki G. The epigenetic effects of antidepressant treatment on human prefrontal cortex BDNF expression. *Int J Neuropsychopharmacol* 2011; **14**: 427–429.
 - 116 Alt SR, Turner JD, Klok MD, Meijer OC, Lakke EAJF, DeRijk RH *et al*. Differential expression of glucocorticoid receptor transcripts in major depressive disorder is not epigenetically programmed. *Psychoneuroendocrinology* 2010; **35**: 544–556.
 - 117 McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M *et al*. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009; **12**: 342–348.
 - 118 Ewald ER, Wand GS, Seifuddin F, Yang X, Tamashiro KL, Potash JB *et al*. Alterations in DNA methylation of Fkbp5 as a determinant of blood–brain correlation of glucocorticoid exposure. *Psychoneuroendocrinology* 2014; **44**: 112–122.
 - 119 Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM *et al*. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci* 2013; **16**: 33–41.
 - 120 Walton E, Hass J, Liu J, Roffman JL, Bernardoni F, Roessner V *et al*. Correspondence of DNA Methylation Between Blood and Brain Tissue and Its Application to Schizophrenia Research. *Schizophr Bull* 2016; **42**: 406–414.
 - 121 Mulligan C, D'Errico N, Stees J, Hughes D. Methylation changes at *NR3C1* in newborns associate with maternal prenatal stress exposure and newborn birth weight. *Epigenetics* 2012; **7**: 853–857.

- 122 Radtke KM, Ruf M, Gunter HM, Dohrmann K, Schauer M, Meyer A *et al.* Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor. *Transl Psychiatry* 2011; **1**: e21.
- 123 Katz ER, Stowe ZN, Newport DJ, Kelley ME, Pace TW, Cubells JF *et al.* Regulation of mRNA expression encoding chaperone and co-chaperone proteins of the glucocorticoid receptor in peripheral blood: association with depressive symptoms during pregnancy. *Psychol Med* 2012; **42**: 943–956.
- 124 Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A *et al.* Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science* 1997; **277**: 1659–62.
- 125 Laplante P, Diorio J, Meaney MJ. Serotonin regulates hippocampal glucocorticoid receptor expression via a 5-HT7 receptor. *Brain Res Dev Brain Res* 2002; **139**: 199–203.
- 126 Weaver ICG, D'Alessio AC, Brown SE, Hellstrom IC, Dymov S, Sharma S *et al.* The transcription factor nerve growth factor-inducible protein a mediates epigenetic programming: altering epigenetic marks by immediate-early genes. *J Neurosci* 2007; **27**: 1756–68.
- 127 Anacker C, Cattaneo A, Luoni A, Musaelyan K, Zunszain PA, Milanese E *et al.* Glucocorticoid-Related Molecular Signaling Pathways Regulating Hippocampal Neurogenesis. *Neuropsychopharmacology* 2013; **38**: 872–883.
- 128 Anacker C, Cattaneo A, Musaelyan K, Zunszain PA, Horowitz M, Molteni R *et al.* Role for the kinase SGK1 in stress, depression, and glucocorticoid effects on hippocampal neurogenesis. *Proc Natl Acad Sci* 2013; **110**: 8708–8713.
- 129 Seth S, Lewis AJ, Saffery R, Lappas M, Galbally M. Maternal Prenatal Mental Health and Placental 11 β -HSD2 Gene Expression: Initial Findings from the Mercy Pregnancy and Emotional Wellbeing Study. *Int J Mol Sci* 2015; **16**: 27482–96.
- 130 O'Donnell KJ, Bugge Jensen A, Freeman L, Khalife N, O'Connor TG, Glover V. Maternal prenatal anxiety and downregulation of placental 11 β -HSD2. *Psychoneuroendocrinology* 2012; **37**: 818–26.
- 131 Mikelson C, Kovach MJ, Troisi J, Symes S, Adair D, Miller RK *et al.* Placental 11 β -Hydroxysteroid dehydrogenase type 2 expression: Correlations with birth weight and placental metal concentrations. *Placenta* 2015; **36**: 1212–7.
- 132 Holmes MC, Abrahamsen CT, French KL, Paterson JM, Mullins JJ, Seckl JR. The Mother or the Fetus? 11 β -Hydroxysteroid Dehydrogenase Type 2 Null Mice Provide Evidence for Direct Fetal Programming of Behavior by Endogenous Glucocorticoids. *J Neurosci* 2006; **26**: 3840–3844.
- 133 Welberg LAM, Seckl JR, Holmes MC. Inhibition of 11 β -hydroxysteroid dehydrogenase, the foeto-placental barrier to maternal glucocorticoids, permanently programs amygdala GR mRNA expression and anxiety-like behaviour in the offspring. *Eur J Neurosci* 2000; **12**: 1047–1054.
- 134 Montano MM, Wang MH, vom Saal FS. Sex differences in plasma corticosterone in mouse fetuses are mediated by differential placental transport from the mother and eliminated by maternal adrenalectomy or stress. *J Reprod Fertil* 1993; **99**: 283–90.
- 135 Lester BM, Marsit CJ, Giarraputo J, Hawes K, LaGasse LL, Padbury JF. Neurobehavior related

- to epigenetic differences in preterm infants. *Epigenomics* 2015; **7**: 1123–36.
- 136 Magiakou MA, Mastorakos G, Rabin D, Dubbert B, Gold PW, Chrousos GP. Hypothalamic corticotropin-releasing hormone suppression during the postpartum period: implications for the increase in psychiatric manifestations at this time. *J Clin Endocrinol Metab* 1996; **81**: 1912–7.
 - 137 Pariante CM, Nemeroff CB. Unipolar depression. In: *Handbook of clinical neurology*. 2012, pp 239–249.
 - 138 Engineer N, Darwin L, Nishigandh D, Ngianga-Bakwin K, Smith SC, Grammatopoulos DK. Association of glucocorticoid and type 1 corticotropin-releasing hormone receptors gene variants and risk for depression during pregnancy and post-partum. *J Psychiatr Res* 2013; **47**: 1166–1173.
 - 139 Stergiakouli E, Sterne JAC, Smith GD. Letter to editor: Failure to replicate the association of glucocorticoid and type 1 corticotropin-releasing hormone receptors gene variants with risk of depression during pregnancy and post-partum reported by Engineer et al. (2013). *J Psychiatr Res* 2014; **56**: 168–170.
 - 140 Li XQ, Zhu P, Myatt L, Sun K. Roles of glucocorticoids in human parturition: A controversial fact? *Placenta* 2014; **35**: 291–296.
 - 141 Sasaki A, Liotta AS, Luckey MM, Margioris AN, Suda T, Krieger DT. Immunoreactive corticotropin-releasing factor is present in human maternal plasma during the third trimester of pregnancy. *J Clin Endocrinol Metab* 1984; **59**: 812–4.
 - 142 Meltzer-Brody S. New insights into perinatal depression: pathogenesis and treatment during pregnancy and postpartum. *Dialogues Clin Neurosci* 2011; **13**: 89–100.
 - 143 Osborne S, Biaggi A, Chua TE, Du Preez A, Hazelgrove K, Nikkheslat N *et al*. Antenatal depression programs cortisol stress reactivity in offspring through increased maternal inflammation and cortisol in pregnancy: The Psychiatry Research and Motherhood - Depression (PRAM-D) Study. *Psychoneuroendocrinology* 2018. doi:10.1016/j.psyneuen.2018.06.017.
 - 144 Sandman CA, Wadhwa P, Glynn L, Chicz-Demet A, Porto M, Garite TJ. Corticotrophin-releasing hormone and fetal responses in human pregnancy. *Ann N Y Acad Sci* 1999; **897**: 66–75.
 - 145 Alves E, Fielder A, Ghabriel N, Sawyer M, Buisman-Pijlman FTA. Early social environment affects the endogenous oxytocin system: a review and future directions. *Front Endocrinol (Lausanne)* 2015; **6**: 32.
 - 146 Feldman R, Weller A, Zagoory-Sharon O, Levine A. Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding. *Psychol Sci* 2007; **18**: 965–70.
 - 147 Eapen V, Dadds M, Barnett B, Kohlhoff J, Khan F, Radom N *et al*. Separation anxiety, attachment and inter-personal representations: disentangling the role of oxytocin in the perinatal period. *PLoS One* 2014; **9**: e107745.
 - 148 Skrundz M, Bolten M, Nast I, Hellhammer DH, Meinschmidt G. Plasma Oxytocin Concentration during Pregnancy is associated with Development of Postpartum Depression. *Neuropsychopharmacology* 2011; **36**: 1886–1893.

- 149 Mileva-Seitz V, Steiner M, Atkinson L, Meaney MJ, Levitan R, Kennedy JL *et al.* Interaction between oxytocin genotypes and early experience predicts quality of mothering and postpartum mood. *PLoS One* 2013; **8**: e61443.
- 150 Mah BL, Bakermans-Kranenburg MJ, Van IJzendoorn MH, Smith R. Oxytocin promotes protective behavior in depressed mothers: a pilot study with the enthusiastic stranger paradigm. *Depress Anxiety* 2015; **32**: 76–81.
- 151 Mah BL, Van IJzendoorn MH, Out D, Smith R, Bakermans-Kranenburg MJ. The Effects of Intranasal Oxytocin Administration on Sensitive Caregiving in Mothers with Postnatal Depression. *Child Psychiatry Hum Dev* 2017; **48**: 308–315.
- 152 Mah BL. Oxytocin, Postnatal Depression, and Parenting. *Harv Rev Psychiatry* 2016; **24**: 1–13.
- 153 Kroll-Desrosiers AR, Nephew BC, Babb JA, Guilarte-Walker Y, Moore Simas TA, Deligiannidis KM. Association of peripartum synthetic oxytocin administration and depressive and anxiety disorders within the first postpartum year. *Depress Anxiety* 2017; **34**: 137–146.
- 154 Leng G, Ludwig M. Intranasal Oxytocin: Myths and Delusions. *Biol Psychiatry* 2016; **79**: 243–250.
- 155 Feldman R, Gordon I, Influx M, Gutbir T, Ebstein RP. Parental Oxytocin and Early Caregiving Jointly Shape Children’s Oxytocin Response and Social Reciprocity. *Neuropsychopharmacology* 2013; **38**: 1154–1162.
- 156 Pratt M, Apter-Levi Y, Vakart A, Feldman M, Fishman R, Feldman T *et al.* Maternal Depression and Child Oxytocin Response; Moderation by Maternal Oxytocin and Relational Behavior. *Depress Anxiety* 2015; **32**: 635–646.
- 157 Feldman R, Gordon I, Influx M, Gutbir T, Ebstein RP. Parental oxytocin and early caregiving jointly shape children’s oxytocin response and social reciprocity. *Neuropsychopharmacology* 2013; **38**: 1154–62.
- 158 Atzil S, Hendler T, Feldman R. Specifying the neurobiological basis of human attachment: brain, hormones, and behavior in synchronous and intrusive mothers. *Neuropsychopharmacology* 2011; **36**: 2603–15.
- 159 Strathearn L, Fonagy P, Amico J, Montague PR. Adult attachment predicts maternal brain and oxytocin response to infant cues. *Neuropsychopharmacology* 2009; **34**: 2655–66.
- 160 Heim C, Young LJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Mol Psychiatry* 2009; **14**: 954–958.
- 161 Smearman EL, Almli LM, Conneely KN, Brody GH, Sales JM, Bradley B *et al.* Oxytocin Receptor Genetic and Epigenetic Variations: Association With Child Abuse and Adult Psychiatric Symptoms. *Child Dev* 2016; **87**: 122–34.
- 162 Kimmel M, Clive M, Gispen F, Guintivano J, Brown T, Cox O *et al.* Oxytocin receptor DNA methylation in postpartum depression. *Psychoneuroendocrinology* 2016; **69**: 150–60.
- 163 Unternaehrer E, Bolten M, Nast I, Staehli S, Meyer AH, Dempster E *et al.* Maternal adversities during pregnancy and cord blood oxytocin receptor (*OXTR*) DNA methylation. *Soc Cogn Affect Neurosci* 2016; **11**: 1460–1470.

- 164 Cecil CAM, Lysenko LJ, Jaffee SR, Pingault J-B, Smith RG, Relton CL *et al.* Environmental risk, Oxytocin Receptor Gene (OXTR) methylation and youth callous-unemotional traits: a 13-year longitudinal study. *Mol Psychiatry* 2014; **19**: 1071–1077.
- 165 Unternaehrer E, Luers P, Mill J, Dempster E, Meyer AH, Staehli S *et al.* Dynamic changes in DNA methylation of stress-associated genes (OXTR, BDNF) after acute psychosocial stress. *Transl Psychiatry* 2012; **2**: e150.
- 166 Henriques TP, Szawka RE, Diehl LA, de Souza MA, Corrêa CN, Aranda BCC *et al.* Stress in Neonatal Rats with Different Maternal Care Backgrounds: Monoaminergic and Hormonal Responses. *Neurochem Res* 2014; **39**: 2351–2359.
- 167 Champagne FA, Meaney MJ. Stress during gestation alters postpartum maternal care and the development of the offspring in a rodent model. *Biol Psychiatry* 2006; **59**: 1227–35.
- 168 Sabihi S, Dong SM, Duroske NE, Leuner B. Oxytocin in the medial prefrontal cortex regulates maternal care, maternal aggression and anxiety during the postpartum period. *Front Behav Neurosci* 2014; **8**: 258.
- 169 Bale TL, Davis AM, Auger AP, Dorsa DM, McCarthy MM. CNS Region-Specific Oxytocin Receptor Expression: Importance in Regulation of Anxiety and Sex Behavior. <http://www.jneurosci.org/content/jneuro/21/7/2546.full.pdf> (accessed 19 Mar2017).
- 170 Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR. Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry* 2000; **157**: 924–30.
- 171 Mehta D, Newport DJ, Frishman G, Kraus L, Rex-Haffner M, Ritchie JC *et al.* Early predictive biomarkers for postpartum depression point to a role for estrogen receptor signaling. *Psychol Med* 2014; **44**: 2309–22.
- 172 Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky ZA. Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. *Mol Psychiatry* 2014; **19**: 560–7.
- 173 McCarthy MM, McDonald CH, Brooks PJ, Goldman D. An Anxiolytic Action of Oxytocin is Enhanced by Estrogen in the Mouse. *Physiol Behav* 1996; **60**: 1209–1215.
- 174 Young LJ, Wang Z, Donaldson R, Rissman EF. Estrogen receptor alpha is essential for induction of oxytocin receptor by estrogen. *Neuroreport* 1998; **9**: 933–6.
- 175 Champagne F, Diorio J, Sharma S, Meaney MJ. Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. *Proc Natl Acad Sci U S A* 2001; **98**: 12736–41.
- 176 Qiu A, Anh TT, Li Y, Chen H, Rifkin-Grabo A, Broekman BFP *et al.* Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. *Transl Psychiatry* 2015; **5**: e508.
- 177 Soe NN, Wen DJ, Poh JS, Chong Y-S, Broekman BF, Chen H *et al.* Perinatal maternal depressive symptoms alter amygdala functional connectivity in girls. *Hum Brain Mapp* 2017. doi:10.1002/hbm.23873.
- 178 Buss C, Davis EP, Muftuler LT, Head K, Sandman CA. High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6-9-year-old children. *Psychoneuroendocrinology* 2010; **35**: 141–53.

- 179 Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology* 2008; **33**: 693–710.
- 180 Sandman CA, Buss C, Head K, Davis EP. Fetal Exposure to Maternal Depressive Symptoms Is Associated With Cortical Thickness in Late Childhood. *Biol Psychiatry* 2015; **77**: 324–334.
- 181 Field T, Diego M, Dieter J, Hernandez-Reif M, Schanberg S, Kuhn C *et al.* Prenatal depression effects on the fetus and the newborn. *Infant Behav Dev* 2004; **27**: 216–229.
- 182 Effects of venlafaxine and chronic unpredictable stress on behavior and hippocampal neurogenesis of rat dams. *Neuro Endocrinol Lett* 2017; **38**: 19–26.
- 183 Talati A, Odgerel Z, Wickramaratne PJ, Weissman MM. Brain derived neurotrophic factor moderates associations between maternal smoking during pregnancy and offspring behavioral disorders. *Psychiatry Res* 2016; **245**: 387–391.
- 184 Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ *et al.* Candidate Genes Expression Profile Associated with Antidepressants Response in the GENDEP Study: Differentiating between Baseline ‘Predictors’ and Longitudinal ‘Targets’. *Neuropsychopharmacology* 2013; **38**: 377–385.
- 185 Van den Hove DLA, Steinbusch HWM, Scheepens A, Van de Berg WDJ, Kooiman LAM, Boosten BJG *et al.* Prenatal stress and neonatal rat brain development. *Neuroscience* 2006; **137**: 145–55.
- 186 Roceri M, Hendriks W, Racagni G, Ellenbroek BA, Riva MA. Early maternal deprivation reduces the expression of BDNF and NMDA receptor subunits in rat hippocampus. *Mol Psychiatry* 2002; **7**: 609–16.
- 187 Wang Q, Shao F, Wang W. Maternal separation produces alterations of forebrain brain-derived neurotrophic factor expression in differently aged rats. *Front Mol Neurosci* 2015; **8**: 49.
- 188 Leff-Gelman P, Mancilla-Herrera I, Flores-Ramos M, Cruz-Fuentes C, Reyes-Grajeda JP, García-Cuétara MDP *et al.* The Immune System and the Role of Inflammation in Perinatal Depression. 2016.
- 189 Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology* 2012; **37**: 137–62.
- 190 Krause D, Jobst A, Kirchberg F, Kieper S, Härtl K, Kästner R *et al.* Prenatal immunologic predictors of postpartum depressive symptoms: a prospective study for potential diagnostic markers. 2014; **264**. doi:10.1007/s00406-014-0494-8.
- 191 Danese A, Caspi A, Williams B, Ambler A, Sugden K, Mika J *et al.* Biological embedding of stress through inflammation processes in childhood. *Mol Psychiatry* 2011; **16**: 244–6.
- 192 Carvalho LA, Torre JP, Papadopoulos AS, Poon L, Juruena MF, Markopoulou K *et al.* Lack of clinical therapeutic benefit of antidepressants is associated overall activation of the inflammatory system. *J Affect Disord* 2013; **148**: 136–140.
- 193 Hepgul N, Cattaneo A, Agarwal K, Baraldi S, Borsini A, Bufalino C *et al.* Transcriptomics in Interferon- α -Treated Patients Identifies Inflammation-, Neuroplasticity- and Oxidative Stress-

- Related Signatures as Predictors and Correlates of Depression. *Neuropsychopharmacology* 2016; **41**: 2502–2511.
- 194 Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Arch Gen Psychiatry* 2008; **65**: 409–15.
 - 195 Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry* 2009; **65**: 732–41.
 - 196 Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A *et al.* Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry* 2001; **58**: 445–52.
 - 197 Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc Natl Acad Sci* 2007; **104**: 1319–1324.
 - 198 Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor- α . *Mol Psychiatry* 2016; **21**: 642–649.
 - 199 Pace TWW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH *et al.* Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am J Psychiatry* 2006; **163**: 1630–3.
 - 200 Du Preez A, Leveson J, Zunszain PA, Pariante CM. Inflammatory insults and mental health consequences: does timing matter when it comes to depression? *Psychol Med* 2016; **46**: 2041–2057.
 - 201 Christian LM. Effects of stress and depression on inflammatory immune parameters in pregnancy. *Am J Obstet Gynecol* 2014; **211**: 275–277.
 - 202 Corwin EJ, Pajer K, Paul S, Lowe N, Weber M, McCarthy DO. Bidirectional psychoneuroimmune interactions in the early postpartum period influence risk of postpartum depression. *Brain Behav Immun* 2015; **49**: 86–93.
 - 203 Walsh K, Basu A, Werner E, Lee S, Feng T, Osborne LM *et al.* Associations Among Child Abuse, Depression, and Interleukin-6 in Pregnant Adolescents. *Psychosom Med* 2016; **78**: 920–930.
 - 204 Shelton MM, Schminkey DL, Groer MW. Relationships Among Prenatal Depression, Plasma Cortisol, and Inflammatory Cytokines. *Biol Res Nurs* 2015; **17**: 295–302.
 - 205 Edvinsson Å, Bränn E, Hellgren C, Freyhult E, White R, Kamali-Moghaddam M *et al.* Lower inflammatory markers in women with antenatal depression brings the M1/M2 balance into focus from a new direction. *Psychoneuroendocrinology* 2017; **80**: 15–25.
 - 206 Graham AM, Rasmussen JM, Rudolph MD, Heim CM, Gilmore JH, Styner M *et al.* Maternal Systemic Interleukin-6 During Pregnancy Is Associated With Newborn Amygdala Phenotypes and Subsequent Behavior at 2 Years of Age. *Biol Psychiatry* 2018; **83**: 109–119.
 - 207 Mondelli V, Cattaneo A, Murri MB, Di Forti M, Handley R, Hepgul N *et al.* Stress and Inflammation Reduce Brain-Derived Neurotrophic Factor Expression in First-Episode Psychosis. *J Clin Psychiatry* 2011; **72**: 1677–1684.
 - 208 Mondelli V, Ciufolini S, Belvederi Murri M, Bonaccorso S, Di Forti M, Giordano A *et al.* Cortisol and Inflammatory Biomarkers Predict Poor Treatment Response in First Episode Psychosis.

Schizophr Bull 2015; **41**: 1162–1170.

- 209 Bergink V, Burgerhout KM, Weigelt K, Pop VJ, de Wit H, Drexhage RC *et al*. Immune system dysregulation in first-onset postpartum psychosis. *Biol Psychiatry* 2013; **73**: 1000–7.
- 210 Veen C, Myint AM, Burgerhout KM, Schwarz MJ, Schütze G, Kushner SA *et al*. Tryptophan pathway alterations in the postpartum period and in acute postpartum psychosis and depression. *J Affect Disord* 2016; **189**: 298–305.
- 211 Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008; **9**: 46–56.
- 212 Wirleitner B, Neutrauer G, Schröcksnadel K, Frick B, Fuchs D. Interferon-gamma-induced conversion of tryptophan: immunologic and neuropsychiatric aspects. *Curr Med Chem* 2003; **10**: 1581–91.
- 213 Badawy AA-B. Tryptophan metabolism, disposition and utilization in pregnancy. *Biosci Rep* 2015; **35**. doi:10.1042/BSR20150197.
- 214 Widner B, Ledochowski M, Fuchs D. Interferon-gamma-induced tryptophan degradation: neuropsychiatric and immunological consequences. *Curr Drug Metab* 2000; **1**: 193–204.
- 215 Cattaneo A, Macchi F, Plazzotta G, Veronica B, Bocchio-Chiavetto L, Riva MA *et al*. Inflammation and neuronal plasticity: a link between childhood trauma and depression pathogenesis. *Front Cell Neurosci* 2015; **9**: 40.
- 216 Plant DT, Pawlby S, Sharp D, Zunszain PA, Pariante CM. Prenatal maternal depression is associated with offspring inflammation at 25 years: a prospective longitudinal cohort study. *Transl Psychiatry* 2016; **6**: e936.
- 217 Su K-P, Huang S-Y, Chiu T-H, Huang K-C, Huang C-L, Chang H-C *et al*. Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2008; **69**: 644–51.
- 218 Mozurkewich EL, Clinton CM, Chilimigras JL, Hamilton SE, Allbaugh LJ, Berman DR *et al*. The Mothers, Omega-3, and Mental Health Study: a double-blind, randomized controlled trial. *Am J Obstet Gynecol* 2013; **208**: 313.e1–313.e9.
- 219 Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P *et al*. Effect of DHA Supplementation During Pregnancy on Maternal Depression and Neurodevelopment of Young Children. *JAMA* 2010; **304**: 1675.
- 220 Borsini A, Alboni S, Horowitz MA, Tojo LM, Cannazza G, Su K-P *et al*. Rescue of IL-1 β -induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. *Brain Behav Immun* 2017; **65**: 230–238.
- 221 Chlodzinska N, Gajerska M, Bartkowska K, Turlejski K, Djavadian RL. Lipopolysaccharide injected to pregnant mice affects behavior of their offspring in adulthood. *Acta Neurobiol Exp (Wars)* 2011; **71**: 519–27.
- 222 Depino AM. Early prenatal exposure to LPS results in anxiety- and depression-related behaviors in adulthood. *Neuroscience* 2015; **299**: 56–65.
- 223 Bakos J, Duncko R, Makatsori A, Pirnik Z, Kiss A, Jezova D. Prenatal Immune Challenge Affects

- Growth, Behavior, and Brain Dopamine in Offspring. *Ann N Y Acad Sci* 2004; **1018**: 281–287.
- 224 Posillico CK, Schwarz JM. An investigation into the effects of antenatal stressors on the postpartum neuroimmune profile and depressive-like behaviors. *Behav Brain Res* 2016; **298**: 218–228.
 - 225 Bronson SL, Bale TL. Prenatal Stress-Induced Increases in Placental Inflammation and Offspring Hyperactivity Are Male-Specific and Ameliorated by Maternal Antiinflammatory Treatment. *Endocrinology* 2014; **155**: 2635–2646.
 - 226 Diz-Chaves Y, Astiz M, Bellini MJ, Garcia-Segura LM. Prenatal stress increases the expression of proinflammatory cytokines and exacerbates the inflammatory response to LPS in the hippocampal formation of adult male mice. *Brain Behav Immun* 2013; **28**: 196–206.
 - 227 Diz-Chaves Y, Pernía O, Carrero P, Garcia-Segura LM. Prenatal stress causes alterations in the morphology of microglia and the inflammatory response of the hippocampus of adult female mice. *J Neuroinflammation* 2012; **9**: 580.
 - 228 Vanbesien-Mailliot CCA, Wolowczuk I, Mairesse J, Viltart O, Delacre M, Khalife J *et al.* Prenatal stress has pro-inflammatory consequences on the immune system in adult rats. *Psychoneuroendocrinology* 2007; **32**: 114–124.
 - 229 Ślusarczyk J, Trojan E, Głombik K, Chamera K, Roman A, Budziszewska B *et al.* Fractalkine Attenuates Microglial Cell Activation Induced by Prenatal Stress. *Neural Plast* 2016; **2016**: 1–11.
 - 230 Ślusarczyk J, Trojan E, Wydra K, Głombik K, Chamera K, Kucharczyk M *et al.* Beneficial impact of intracerebroventricular fractalkine administration on behavioral and biochemical changes induced by prenatal stress in adult rats: Possible role of NLRP3 inflammasome pathway. *Biochem Pharmacol* 2016; **113**: 45–56.
 - 231 Barnes J, Mondelli V, Pariante CM. Genetic Contributions of Inflammation to Depression. *Neuropsychopharmacology* 2016. doi:10.1038/npp.2016.169.

Table 1: Summary of research findings from large cohorts relating to offspring outcome as a result of depression in the perinatal period.

Offspring Outcome Factor	Antenatal Depression		Postnatal Depression	
	Study Details	Findings	Study Details	Findings
Internalising Behaviour	Generation-R, n=2698	Associated with internalising behaviour at 3 years, as shown by emotional reactivity, anxiety/depression, somatic complaints and withdrawal ¹⁶ . [OR 1.18 per 1 SD increase (95% CI 1.08;1.29), p<0.001]	TRAILS, n=2729	Significantly associated with internalising difficulties in early adolescence ¹⁹ . [β =0.28 (95%CI 0.14;0.41), p<0.001]
Externalising Behaviour	Generation-R, n=2698	Associated with child externalising difficulties, such as attention problems and aggressive behaviour ¹⁶ . [OR 1.19 (95% CI 1.09;1.30), p<0.001]	ALSPAC, n=3298	Associated with offspring externalising behaviour such as inattention and hyperactivity ¹¹ . [R^2 =0.09, p<0.05]
	Generation-R, n=2280; ALSPAC, n=3442	Higher risk of child attention problems ¹⁷ . [OR 1.23, (95% CI 1.05;1.43); OR 1.33 (95% CI 1.19;1.48)]	QLSCD, n=2057	Associated with high trajectories of inattention and hyperactivity-impulsivity ¹⁵ . [OR 1.35 (95% CI 1.18;1.54)]
			ALSPAC, n=8598	Increased risk of conduct problems ¹² . [OR 1.74 (95% CI 1.33;2.52)]
			NLSCY, n=10033	Association with physical aggression ¹³ . [OR 2.94, P<0.05]
Emotional Development	ALSPAC, n=2891	Total emotional problems score negatively associated with exposure to antenatal depression, when controlling for psychological and maternal lifestyle variables ⁸ . [β =0.22 (SE 0.07), p<0.01]		

Cognitive Development	ALSPAC, n=5059	Low full-scale IQ scores ⁹ . [SE=0.78, (95% CI 101.57;104.64)]	ALSPAC, n=5059	Low full-scale IQ scores ⁹ . [SE=1.17 (95% CI 104.26;108.84)]
Attachment	Generation-R, n=627	Not associated with attachment insecurity ¹⁸ . [OR 0.96 (95% CI 0.81;1.14)]	Generation-R, n=627	Not associated with infant attachment insecurity ¹⁸ . [OR 0.91 (95% CI 0.75;1.10)]
Adolescent Psychopathology	ALSPAC, n=8937	1 SD increase in maternal EPDS score positively associated with offspring depression aged 18 years, when controlling for maternal lifestyle and depression history ¹⁰ . [OR 1.23 (95% CI 1.03;1.44), p=0.025]	NLSCY, n=937	Infants exposed to depression at 2-3 years and 4-5 years postpartum had a 2-fold increased risk of emotional disorder at 12-13 years ¹⁴ .